

to consider some of the more significant procedures and principles involved in the experimental study of the infection. In the first instance it has brought together into one chapter a consideration of the fluids, secretions and excretions of the tuberculous body. Following this, it enters into an exposition of methods for the detection of the tubercle bacillus by staining, isolation and animal inoculation, and gives a description of this microorganism and compares it with other acid-fast bacteria, and deals with serological diagnosis and with diagnosis by the use of tuberculin. Secondly it devotes a number of chapters to some of the general factors concerned in the infection of animals and the study of experimental tuberculosis. The guiding principle of the author, as expressed in the preface, has been to cover the subject as concisely as is consistent with adequacy of presentation. Therefore, he has sought to present clearly in each of the various parts of the book only so many of the available technical procedures as appeared to him to be commensurate with the immediate subject at hand, always with an eye to the conservation of space and the prevention of too much duplication of essentially similar methods. Of the methods outlined, most have proved dependable through long application, but a few have been included which are new and virtually untried, because selection has occasionally been made on promise and rationale as well as on demonstrated worth. This plan has led to the omission of many methods, some of them of unquestioned value. It was the author's desire to write a book which would be useful to practising physicians, to public health officials and laboratory workers in general and to medical students. Part I deals with the General Consideration of the Body Fluids and Excreta in Tuberculosis. Part II treats of Bacteriologic Diagnosis, with Chapters on the demonstration of the tubercle bacillus by staining methods, by methods of concentration and isolation and by the inoculation of animals and a discussion of the tubercle bacillus its cultivation and the non-pathogenic acid-fast bacteria. Part III treats of Diagnosis by

Use of Tuberculin, with Chapters on tuberculin and its preparation, and the diagnostic application of tuberculin, Part IV treats of Serological Diagnosis with Chapters on the Tuberculo-Complement Fixation and other Serological tests, Part V treats of Methods of Value in Studies of Tuberculosis Experimentally Produced, with Chapters on the inoculation of animals with the tubercle bacillus, induced tuberculosis in animals, methods of studying induced tuberculosis in animals, and histologic technique, while the final chapter treats of the equipment for a tuberculosis laboratory, with bibliography and index. The author has performed a most useful service in bringing together the various laboratory procedures that are concerned with the diagnosis and treatment of tuberculosis, as well as those adapted to research work in tuberculosis. It appears on inspection to have achieved most acceptably the aim set forth in the author's preface. A good word may be said for the new publishing house of Charles C. Thomas in the general excellence of this production both as to printing and binding. It is a very neat job.

*The Pressure Pulses in the Cardiovascular System Monograph on Physiology* By CARL J. WIGGERS, M. D., Professor of Physiology in the School of Medicine of Western Reserve University, Cleveland, Ohio. 200 pages, with diagrams and illustrations. Longmans, Green and Co. London-New York-Toronto, 1928. Price \$5.00.

The book is dedicated to Graham Lusk. Its object has been the analysis, in the briefest manner possible, of the present status of our knowledge concerning the pressure of our knowledge concerning the pressure pulses in the cardiovascular system. Apparatus for making cardiodynamic studies comparable in accuracy to physical instruments used for other types of physiological investigation has been available for a comparatively short time only. Its use under controlled experimental conditions demands a specialized technique and the evaluation of records must be tempered by an insight gained only by years of service. Consequently this important method for investi-





junctions. Some subcutaneous and muscular hemorrhage was almost always present, while duodenal, cecal, vesical and paravesical hemorrhages were common. The minute morphology showed hemorrhages in all parts of the body except in the gums and joints. There was a marked fatty infiltration and degeneration of the liver, kidneys, adrenals, and even in the lungs and the peribronchial cartilages, the pancreas, skeletal muscles and the blood walls. Degenerative changes other than fatty, resulting in the complete loss of substance, were observed in the cartilages, bones, teeth, muscles, many of the glandular organs, as well as in the central, peripheral and sympathetic nervous systems. This widely distributed liquefaction of the cytoplasm and cell walls results in destruction of cartilage cells and of the cartilaginous matrix, at least in the costal cartilages, in the detachment of the periosteum and peridontia, in reduction in caliber of the bones, and in both the caliber and the length of the implanted portions of the teeth. It may effect not only the separation of ununited epiphyses and loosening of the teeth but the complete destruction of the parenchyma of some areas in the glandular and other organs, in desquamation of the mucosa and renal epithelium, and in complete disintegration

of the walls of blood vessels. In addition to the fatty and lytic changes, coagulative changes, such as extreme waxy degeneration in the muscles, were also noted in glandular and nervous tissues. The only proliferative changes noted occurred in the costal cartilages and concerned an increase in caliber at the region of the costochondral junctions and an invasion of connective tissue into areas of degeneration. Necrotic areas on the surface and in the substance of the liver were occasionally observed, but may be wholly unrelated to scurvy. Vacuolation was common to many organs, and fenestration up to a marked degree was observed, especially in muscle, bone marrow, the pulp of the teeth, and also in the cord and brain. Definite cytological changes occurred in the blood of guinea pigs in experimental scurvy. These changes became evident after ten days on the scorbutic diet. They consist of a decrease in red cells, hemoglobin and color index, and apparent decrease in fragility, a relative decrease in the number of lymphocytes, an absolute increase in the polymorphonuclears, and an increase in reticulated and nucleated red blood cells and leukocytes. The eosinophile, basophile, monocyte and transitional cell counts were not considered characteristic of scurvy.

# College News Notes

## PROGRAM THIRTEENTH ANNUAL CLINICAL SESSION

### BOSTON COMMITTEES

JAMES H. MEANS, *General Chairman*

### COMMITTEE ON ARRANGEMENTS

JAMES H. MEANS

WILLIAM B. BREED

HENRY A. CHRISTIAN

RANDALL CLIFFORD

CHESTER M. JONES

ELLIOTT P. JOSLIN

ROGER I. LEE

GEORGE R. MINOT

JOHN H. MUSSER

JOHN PHILLIPS

JOSEPH H. PRATT

FRITZ B. TALBOT

CONRAD WESSELHOEFT

FRANKLIN W. WHITE

### COMMITTEE ON HALL

FRANKLIN W. WHITE

### COMMITTEE ON CLINICS

HENRY A. CHRISTIAN

CHESTER M. JONES

ELLIOTT P. JOSLIN

GEORGE R. MINOT

JOSEPH H. PRATT

CONRAD WESSELHOEFT

### COMMITTEE ON ENTERTAINMENT

RANDALL CLIFFORD

WILLIAM B. BREED

FRITZ B. TALBOT

### PRELIMINARY PROGRAM

### ANNUAL CLINICAL SESSION

### THE AMERICAN COLLEGE OF PHYSICIANS

APRIL 8-12, 1929

Monday, April 8, 1929

OPENING SESSION, 2:30 O'CLOCK

Hotel Statler Ballroom

1. Addresses of Welcome: David I. Edsall, Dean of Harvard Medical School; Alexander S. Begg, Dean of Boston University Medical School; A. Warren Stearns, Dean of Tufts College Medical School.

John M. Birnie, President of Massachusetts Medical Society; Lincoln Davis, President of Suffolk District Medical Society.

2. Reply to Addresses of Welcome: Charles F. Martin, President of The American College of Physicians.

3. Tuberculosis: A Collection of Papers by Lawson Brown, State Laboratory.

4 (Title not yet announced) Lewellys F Barker, Baltimore

5 Juvenile Diabetes I M Rabinowitch, Montreal

6 Glycosuria James E. Paullin, Atlanta

7 Clinical Aspects of Paroxysmal Hypertension M C Pincoffs, Baltimore

#### EVENING SESSION, 8 00 O'CLOCK

Hotel Statler Ballroom

#### *Symposium on Deficiency Diseases*

1 The Fundamental Nature of Deficiencies George R. Minot, Boston

2 Pathology of Deficiencies S Burt Wolbach, Boston

3 Biochemistry and Physiology of Deficiencies George R. Cowgill, New Haven

4 Pernicious Anemia Randolph West, New York.

Tuesday, April 9, 1929

MORNING, 9 00 TO 12 00 O'CLOCK

Hospital Clinics

AFTERNOON, 2 30 TO 5 00 O'CLOCK

Hotel Statler Ballroom

1 Fatigue and Infection W L Holman, Toronto

2 Neoplasms J B Murphy, New York

3 Specific Dynamic Action of Protein, Fat and Carbohydrate in Altered States of Nutrition Edward H Mason, Montreal

4 The Relation of Neisserian Infection to the Various Types of Arthritis O H Perry Pepper, Philadelphia

5 The Fallacy of Vaccine Therapy Charles C Bass, New Orleans

6 The Treatment of Angina Pectoris Harlow Brooks, New York

7 The Coronary Problem Arthur R. Elliott, Chicago

8 Clinical Aspects of Trichiniasis Lewis A Conner, New York.

9 An Intensive Clinical Study of a Graphic Method of Recording Blood Pressure Louis F Bishop and Louis F Bishop, New York

#### EVENING SESSION, 8 00 O'CLOCK

Hotel Statler Ballroom

1 Psychiatry in Relation to Medicine Austin F Riggs, Stockbridge, Mass

2 Syphilis of the Adrenals and Its Relationship to the So-called Idiopathic Addison's Disease Aldred S Warthin, Ann Arbor

3 Lung Syphilis R I Rizer, Minneapolis

A smoker will follow this session

Wednesday, April 10, 1929

MORNING, 9 00 TO 12 00 O'CLOCK

Hospital Clinics

AFTERNOON, 2 30 O'CLOCK

Hotel Statler Ballroom

1 The Treatment of General Paresis Harry C Solomon, Boston

2 Psychiatry's Part in Preventive Medicine Arthur H Ruggles, Providence

3 The Need of Emotional Data in the Medical History John Favill, Chicago

4 Milder Forms of Coronary Obstruction James B Herrick, Chicago

5 The Failing Heart of Middle Life David Riesman, Philadelphia

6 Hypertension George C Hale, London, Ont

7 Undulant Fever in the United States George Blumer, New Haven

8 (Title not yet announced) Robert A Cooke, New York

9 Tobacco Smoking and Gastric Symptoms Irving Gray, Brooklyn

#### EVENING SESSION, 8 00 O'CLOCK

Hotel Statler Ballroom

1 Serums and Vaccines in the Prevention and Treatment of Disease. Ben White, Boston

2 Clinico-Roentgenological Conference M C Sosman and Associates, Boston

Thursday, April 11, 1929

MORNING, 9 00 TO 12 00 O'CLOCK

Hospital Clinics

AFTERNOON, 2 30 O'CLOCK

Hotel Statler Ballroom

1 The Treatment of Acute Aspiration Cecil K Drinker, Boston

2. The Significance of Abnormal Metabolic Features in the Management of Thyrotoxicosis Walter W Palmer, New York

3 Can or Will the Internist Practice Preventive Medicine? George H Bigelow, Boston

4 Factors in the Prognosis of High Blood Pressure W W Herrick, New York

5 The Carotid Sinus Reflex (Hering), Its Use in the Diagnosis and Treatment of Certain Cardiovascular Diseases C Saul Danzer, Brooklyn

6 Lead Poisoning from Snuff Raymond J Reitzel, Galveston

The General Business Meeting of The College will be held at 4 00 in the Hotel Statler Ballroom All Masters and Fellows should attend

#### EVENING, 7 00 O'CLOCK

Annual Banquet of The College

To be followed by a Dance

Address George E Vincent, President of Rockefeller Foundation

Friday, April 12, 1929

MORNING, 9 00 to 12 00 O'CLOCK

Hospital Clinics

AFTERNOON, 2 30 O'CLOCK

Hotel Statler Ballroom

1 Motion Picture Demonstrating Its Value in Teaching Electrocardiographic Interpretations of Cardiac Arrhythmias Joseph B Wolfe, Philadelphia

2 Dr William Dunlop and Pioneer Canadian Medicine J W Crane, London, Ont

3 Rheumatic Fever Homer F Swift, New York.

4 (Title not yet announced) J C Meakins, Montreal

5 Results to Be Expected in Malignant Disease Treated by Radiotherapy George E Pfahler, Philadelphia

6 The Problem of the Nervous Patient Charles H Nielson, St Louis

7 Endogenous Obesity—A Misconception L H Newburgh and M W Johnston, Ann Arbor

#### EVENING SESSION, 8 00 O'CLOCK

Hotel Statler Ballroom

Convocation Exercises

The General Profession is cordially invited No special admission tickets are required

1 Convocation Ceremony

2 President's Address Charles F Martin, Montreal

### PRELIMINARY PROGRAM OF SPECIAL CLINICS AND DEMONSTRATIONS

This year the general session will be held in the afternoons and evenings while clinics and demonstrations will be held in the mornings from 9 00 to 12 00

Special Admission Cards required Clinic reservation forms and full directions will accompany the Final Program Reservations may be made by mail or daily at the Registration Bureau

Special clinics and demonstrations will be held as follows

### BETH ISRAEL HOSPITAL

Program in charge of Herrman L Blumgart

## B

## BOSTON CITY HOSPITAL

1 (A guest will give a clinic at this time, the name will be announced later)

2 The Progress of the Boston City Hospital John J Dowling, Superintendent

3 Treatment of Pneumonia Demonstration of Cases Edwin A Locke.

4 Clinic of Unusual Cases Francis W Palfrey.

5 Pernicious Anemia Demonstration of Cases William B Castle

6 Treatment of Anemias Demonstration of Cases George R Minot

WEDNESDAY, APRIL 10, 1929

1 (A guest will give a clinic at this time, the name will be announced later)

2. Gastro-Intestinal Cases Franklin W White

3 Cardiac Cases William H Robey

4 Nephritis Cases William R Ohler

5 The Surgical Treatment of Pulmonary Tuberculosis Demonstration of Cases Edward D Churchill

Hypertension and Arteriosclerosis Demonstration of Cases Soma Weiss

THURSDAY, APRIL 11, 1929

1 Cardiac Cases Edward N Libby and Thomas J O'Brien

2 A Case Illustrating the Value of the Electrocardiogram James M Faulkner

3 Epilepsy William G Lennox.

4 Diseases of the Coronary Vessels Demonstration of Cases Joseph T Wearn.

5 Peptic Ulcer Demonstration of Cases Maurice Fremont-Smith

6 Neurological Cases Stanley Cobb

7 (A guest will give a clinic at this time, the name will be announced later)

FRIDAY, APRIL 12, 1929

1 (A guest will give a clinic at this time, the name will be announced later)

2 Cases of Disease of the Hemopoietic System Ralph C Larrabee.

3 Lymphoblastoma Demonstration of Cases Henry Jackson, Jr

4 Tropical Diseases Demonstration of Cases George C Shattuck.

5 Fluoroscopic Diagnosis in Chest Conditions Demonstration of Cases Harold W Dana

6 Carcinoma of the Head of the Pancreas Demonstration of Cases Irving J Walker

## C

BOSTON CITY HOSPITAL  
THORNDIKE MEMORIAL LABORATORY

WEDNESDAY AND THURSDAY

APRIL 10 AND 11

BETWEEN 10 30 AND 12 30

Demonstration of Researches Concerning the Following Topics

Dr Castle and Associates

Dr Jackson and Associates

Dr Lawrence and Associates

Dr Lennox

Dr Minot and Associates

Dr Nye and Associates

Dr Wearn and Associates

Dr Weiss and Associates

Anemia

Malignant Tumors

The Physiology and Pathology of White Cells

Epilepsy

The Blood

Bacteriological Problems

The Capillaries

Vascular Problems

BOSTON CITY HOSPITAL  
SOUTH DEPARTMENT

Program in charge of Edwin H. Place

Ward visits on (1) diphtheria, (2) scarlet fever, (3) a few of the other minor groups such as chicken pox, mumps, measles and whooping cough

Amphitheater demonstration of cases of chronic laryngeal injury and other damages resulting from contagious diseases

E

## BOSTON DISPENSARY

TUESDAY, APRIL 9, 1929

- |   |  |
|---|--|
| 1 Heart Disease. David Davis                | 4 Chronic Pancreatic Disease. Bert B Hershenson. |
| 2 Essential Hypertonia David Ayman          | 5 Tuberculosis H Louis Kramer                    |
| 3 Neurological Clinic A Warren Stearns      |  |
| 4 Obesity Mark Falcon-Lesses                |  |
| 5 Gastro-Intestinal Clinic Percy B Davidson |  |

THURSDAY, APRIL 11, 1929

- |  |
|--|
| 1 Neurosyphilis Arthur Beck  |
| 2 Neurasthenia Joseph H Kaplan   |
| 3 Nephrosis Tobert W Buck.   |
| 4 Domiciliary Medicine in Clinical Teaching—Selected Case Osadore Olef |
| 5 Domiciliary Medicine in Clinical Teaching—Selected Case Charles Korb |
| 6 Diabetes James H Townsend  |

WEDNESDAY, APRIL 10, 1929

- |                                   |
|-----------------------------------|
| 1 Bronchiectasis William Dameshek |
| 2 Psychalgia Joseph H Pratt       |
| 3 Arthritis John D Adams          |

F

## CHILDREN'S HOSPITAL

Program in charge of Kenneth D. Blackfan

G

HOMEOPATHIC HOSPITAL  
EVANS MEMORIAL CLINIC

TUESDAY, APRIL 9, 1929

- |  |
|--|
| 1 Sterility Clinic. Special Emphasis to be Placed on the Constitutional Factors in Sterility S R Meaker and A W Rowe |
|--|

WEDNESDAY, APRIL 10, 1929

*Endocrine Clinic*

- |  |
|--|
| 1 Endocrine Diagnosis and Therapy Charles H Lawrence   |
| 2 Endocrine Disorders Associated with Otosclerosis and the Meniere Syndrome D W Drury                                |
| 3 Eye Findings in Endocrine Disorders W D Rowland  |
| 4 Cases Presenting Outward Evidence of Endocrine Disorders Found on Study not to have Endocrine Disturbance A W Rowe |

- |  |
|--|
| 5 Dementia Praecox L G Hostins   |
| 6 The Follicular Hormone. J C Janney   |
| 7 Discussion on Sugar Metabolism as Influenced by Insulin in Pituitary Disease H Ulrich and A W Rowe |

THURSDAY, APRIL 11, 1929

*General Medical Clinic*

- |   |
|---|
| 1 Heart Clinic. W D Reid  |
| 2 Intestinal Migraine C W McClure   |
| 3 Neurology A H Garrick   |
| 4 Lung Abscess, Diagnosis and Treatment Bronchoscopy, the Use of the Bronchoscope in Diagnosis and Treatment I R. Johnson |

FRIDAY, APRIL 12, 1929

(Program to be a normal late )

# H MASSACHUSETTS GENERAL HOSPITAL

- 1 Clinic by James E Paullin, Atlanta
- 2 Thoracic Clinic Frederick T Lord
- 3 Cases of Hypertension William B Breed
- 4 Cardiac Clinic Howard B Sprague
- 5 Endocrine Clinic Walter Bauer and Dwight L Sisco

WEDNESDAY, APRIL 10, 1929

- 1 Clinic by Lewellys F Barker, Baltimore.
- 2 Demonstration of Medical Cases William B Robbins
- 3 Pediatric Clinic Fritz B Talbot and Harold L Higgins
- 4 Clinico-pathological conference Richard C Cabot and Tracy B Mallory
- 5 Diabetic Clinic Roy R Wheeler

THURSDAY, APRIL 11, 1929

- 1 Clinic by O H Perry Pepper, Philadelphia
- 2 Neurological Clinic James B Ayer
- 3 Psychotherapy of Gastro-Intestinal Diseases William Herman
- 4 Gastro-Intestinal Clinic Chester M Jones
- 5 Indications for Splenectomy Arhe V Bock
- 6 Cases of Pernicious Anemia Wyman Richardson

FRIDAY, APRIL 12, 1929

- 1 Clinic by J C Meakins, Montreal
- 2 Demonstration of Cases Gerald Blake
- 3 Medical Clinic. James H Means
- 4 Demonstration of Cases F Dennette Adams
- 5 Anaphylaxis Clinic Francis M Rackemann

# I NEW ENGLAND BAPTIST HOSPITAL

Program in charge of Albert A Hornor

# J NEW ENGLAND DEACONESS HOSPITAL

Program in charge of Elliott P Joslin

- 1 Carcinoma of the Colon and Colitis from the Surgical Point of View Daniel F Jones
- 2 Gastro-Intestinal Cases Sara M Jordan and Chester Kiefer
- 3 Thyroid Cases Frank H Lahey
- 4 Pedigreed Diabetics Elliott P Joslin
- 5 Surgery in Diabetics L S McKittrick
- 6 The Pathology of Diabetes Shields Warren

There will be further additions to this program including clinics by larynologists, ophthalmologists, gynecologists and roentgenologists

# K PETER BENT BRIGHAM HOSPITAL

- 1 Diagnosis of Certain Forms of Heart Disease Lewis A Conner, New York.
- 2 Chronic Myocardial Disease Henry A Christian
- 3 Results of Treatment of Duodenal Ulcer E S Emery
- 4 Some Considerations on the Relation of Cardio-Renal System to Surgery of the Urinary Organs William S Quinby
- 5 Bronchoscopy in Lung Disease. Lyman C Richards

WEDNESDAY, APRIL 10, 1929

1 Cardiac Disease, the Result of Infectious Processes James B Herrick, Chicago

2 Gallbladder Disease Channing Frothingham

3 Bronchial Asthma I Chandler Walker

4 Anemia William P Murphy

5 Thrombophlebitis John Homans

THURSDAY, APRIL 11, 1929

1 Mitral Stenosis David Riesman, Philadelphia

2 Signs of Persisting Infection in Acute Rheumatic Fever Clifford L Derick

3 Hemorrhagic Nephritis James P O'Hare

4 A Surgeon's Views of the Treatment of Peptic Ulcer David Cheever

5 Neurosurgical Conditions Harvey Cushing

FRIDAY, APRIL 12, 1929

1 Hypertension Charles F Martin, Montreal

2 Vascular Disease in Diabetes Mellitus Reginald Fitz

3 Treatment of Certain Types of Cardiac Arrhythmia Samuel A Levine

4 Treatment of Trifacial Neuralgia Gilbert Horrax

5 Diuretics Henry A Christian

L

## ROBERT BRECK BRIGHAM HOSPITAL

Program in charge of Louis M Spears  
Clinics on Arthritis

M

## UNITED STATES NAVAL HOSPITAL

Program in charge of Capt F L Pleadwell, MC, U S N

Presentation of medical cases in the conference room of the hospital each morning. Following this the group will be split up in sections of five. Each section will be in charge of a ward medical officer, and the balance of the morning will be devoted to ward rounds.

## TECHNICAL EXHIBIT

The technical exhibits have been arranged by the Executive Secretary, Mr E R Loveland, and the following chart shows the arrangement of booths and the assignment to exhibitors from various parts of the country. The exhibits are highly diversified in their variety and will bring to the attendants at the Clinical Session, the latest and most improved equipment, the best pharmaceutical products, almost the whole library of medical publications and many other products of special interest to the Internist, Pediatrician, Neurologist, Psychiatrist, Radiologist and research worker.

This Exhibit is undoubtedly the best arranged and the most popular one that The College has yet had. The location is in the Ballroom Foyer where all attendants to the meeting will pass through the exhibits daily. The Joseph T Griffin Decorating Company, of Louisville, Kentucky, who installed the exhibits for the American Medical Association, the Southern Medical Association and many other prominent medical societies, will be in charge of the booths and decorations.





## LIST OF EXHIBITORS

SPACE	NAME	CITY AND STATE	Product
20	Abbott Laboratories	North Chicago, Ill	Pharmaceutical Products
12 & 21	D Appleton & Company	New York, N Y	Medical Publications
31	The Battle Creek Food Company	Battle Creek, Mich	Health Foods
22	Bausch & Lomb Optical Co	Rochester, N Y	Microscopes, Photomicro & Projection Apparatus
40	P Blakiston's Son & Co	Philadelphia, Pa	Medical Publications
13	The Borden Sales Company, Inc.	New York, N Y	Merrell Soule Infant Foods
26	Britesun, Inc.	Chicago, Ill	Therapeutic Lamps
25	Cambridge Instrument Co, Inc	New York, N Y	Electrocardiographs & Accessories, and other Physiological Instruments
3	Cameron's Surgical Specialty Co	Chicago, Ill	Electro-Diagnostic Surgical & Dental Instruments
44	G W Carnrick Co	Newark, N J	Pharmaceutical Products
1	Warren E Collins, Inc	Boston, Mass	Roth-Barach Oxygen Apparatus
14	F A Davis Company	Philadelphia, Pa	Medical Publications
16	Deshell Laboratories, Inc.	Chicago, Ill	"Petrolagar"
42 & 43	General X-Ray Company	Boston, Mass	"Morse" Wave Generator, GX-Galvane-Faradic Plate, Diathermy Apparatus, Electrodes
34	Paul B Hoeber, Inc	New York, N Y	Medical Publications
19	Horlick's Malted Milk Corporation	Racine, Wis	Malted Milk Products
17	Kalak Water Company, Inc	New York, N Y	Kalak Water
4	Charles B Knox Gelatine Co, Inc	Johnstown, N Y	Knox Gelatine
15	Lavoris Chemical Company	Minneapolis, Minn.	"Lavoris"
15	LaMotte Chemical Products Co	Baltimore, Md	LaMotte Blood Chemistry Outfits
30	Ica & Febiger	Philadelphia, Pa.	Medical Publications
9	J B Lippincott Company	Philadelphia, Pa	Medical Publications

27	MacGregor Instrument Company	Needham, Mass	Vim Stainless Steel Needles, Vim Emerald Luer Syringes, Vim Surgical & Medical Specialties Medical Publications
8	The Macmillan Company	New York, N Y	
2	L F Mahady Company	Boston, Mass	Anaesthetic Apparatus, Laboratory Equipment, Diagnostic & Scientific Apparatus, Vaccines, Intravenous Products, Orthopedic Appliances & Supplies, Instruments for Operating Room, E F M Catgut
18	The Medical Protective Company	Chicago, Ill	Malpractice Insurance
24	Mellin's Food Company	Boston, Mass	Mellin's Food
38	Merek & Company, Inc	Rahway, N J	Pharmaceutical Products
23	The Wm S Merrell Company	Cincinnati, Ohio	Pharmaceutical Products
32 & 37	Merrell Soule Company	New York, N Y	Infant Foods
35	The C V Mosby Company	St. Louis, Mo	Medical Publications
39	Thomas Nelson & Sons	New York, N Y	Medical Publications
28	The E L Patch Company	Boston, Mass	Cod Liver Oil
6	Pittsburgh Plate Glass Co	Pittsburgh, Pa	"Helioglass"
7	Richards, Inc	Glenolden, Pa.	Psyllium Seed & Acidophilus Products
11	W B Saunders Company	Philadelphia, Pa	Medical Publications
27	Sanborn Company	Cambridge, Mass	"Graphic" Metabolism Apparatus
11	Spencer Lens Company	Boston, Mass	Optical Instruments, Projection Apparatus, Laboratory Equipment
50	Swann-Myers Co	Indianapolis, Ind	Pollens, Ephedrine Preparations, Dextrose Ampoules and other Pharmaceutical Products
16	Tailby-Nason Company	Boston, Mass	Cod Liver Oil
5 & 10	Victor X-Ray Corporation	Chicago, Ill	Electrocardiograph & Quartz Lamps
11	{ Winthrop Chemical Company, Inc H A Metz Laboratories, Inc	New York, N Y	Pharmaceutical Products

## THE MACMILLAN COMPANY

Booth 8

The Macmillan Company will display at Booth 8 a long list of recent and important medical books for the Internist. There are few other opportunities when one may leisurely look over the medical publications, past and recent, as at the Exhibit of this Clinical Session. Macmillan's announcements may also be found on page one of the Advertising Section of this journal.

## MERRELL SOULE COMPANY

Booths 32-37

Merrell-Soule Powdered Protein Milk is the dehydrated equivalent of Finkelstein's original Eiweissmilch and should not be confused with calcium caseinate or other preparations used in preparing a formula high in protein. The removal of a large proportion of the whey and retention of the lactic acid producing organisms in a viable condition contributes very largely to the product's therapeutic value. The wealth of clinical evidence accumulated in recent years compels us to submit that protein milk, as well as being ideal for, is the food of choice for the premature infant and for those types of nutritional disturbances characterized by hydrolability and inability to digest or assimilate normal formulae with consequent failure to gain. Samples and literature may be obtained by calling at the booths of the Merrell-Soule Company at the Exhibit during the Clinical Session.

## LEA &amp; FEBIGER

Booth 30

At Booth 30, Lea & Febiger will exhibit medical books of all descriptions, several by Fellows of The College. Orders may also be placed with them for subscription to the oldest medical journal in America devoted to Medicine, *The American Journal of Medical Sciences*. Lea & Febiger's announcements of publications may be found on page 8 of the Advertising Section of this journal.

## DASHELL LABORATORIES, INC

Booth 16

Petrolagar, the emulsion for use in place of plain mineral oil will be interestingly displayed at the meeting in Boston, April 8-12.

## KALAK WATER COMPANY

Booth 17

The Kalak Water Company will exhibit at Booth 17 "Kalak Water," made of distilled water and chemically pure salts of the kind normally present in the body. Kalak Water is non-laxative and higher in available alkali and richer in Calcium than any natural or artificial water known.

## D APPLETON &amp; COMPANY

Booths 12-21

A long list of important medical books and publications will be exhibited at the double booth of D Appleton & Company, where will be found a number of courteous men fully conversant with the field of medical publications to give you information and to show you the publications of this Company.

## THE BATTLE CREEK FOOD COMPANY

Booth 31

"Lacto-Dextrin," a special colon food for changing the intestinal flora to combat auto-intoxication, will be one of the products exhibited at Booth 31 by The Battle Creek Food Company. Their various pamphlets concerning all of their products will be gladly sent upon request.

## BAUSCH &amp; LOMB CO

Booth 22

Among the most important instruments which are universally used in the physician's laboratory throughout the world is the microscope. It has become a necessity for the study of bacteriology and pathology, for the making of bloodcounts and performing numerous other functions which make the medical practice what it is today.

Because of its fine resolution and high magnification, the Bausch & Lomb FFSA-8 Microscope is the instrument which enjoys the greatest popularity and has been chosen by the members of the medical profession as their laboratory instrument. This "Physicians' Microscope," as it is popularly designated, is an ideal instrument for bacteriological work. Its 43X (4mm) long working distance objective is unequalled for work with the haemacytometer.

The FFSA-8 is provided with a 10X and a 43X objective and a 97X oil immersion objective for high power work. These objectives together with the 5X and 10X Huygenian eyepieces furnish a range from fifty to about one thousand times. Each of these objectives is mounted in standardized mounts, the lens elements being exactly set in threadless cells, so that precise centering of the lens element is assured.

The latest improvement of this Physicians' Microscope is the built-on mechanical stage which is indispensable in blood counting and offers a means for systematically examining a 50 by 75mm slide.

The FFSA-8 is regularly equipped with a divisible Abbe condenser, B & L Patented side fine adjustment and an improved rack and pinion substage.

This microscope is to be on exhibition at the meeting of The American College of Physicians in April, 1929. A detailed explanation and demonstration will be given at that time.

## THE WM S MERRELL COMPANY

Booth 23

Among products exhibited by The Wm S Merrell Company will be "Lacrimin," described as "milk of castor oil." This product is a thick creamy substance, perfectly emulsified, looking and tasting like whipped cream, but retaining the full effects of the castor oil, without its taste. Undoubtedly, such a product will find a warm welcome among physicians and patients other than children, for it happens all too often that a salt or pill is surreptitiously substituted for the castor oil prescription, even where the latter may be essential for correct results. Lacrimin can be prescribed without the patient being aware of the fact that he (or in the obstreperous case probably more often "she") is to take castor oil.

"It's Not the Cost—It's the Upkeep" is the title of an amusing little circular recently issued by The Wm S Merrell Company, depicting graphically the numerous "bribes" offered by fond parents to their unruly offspring refusing to take the "nasty castor oil" that the doctor prescribed.

## P BLAKISTON'S SON &amp; CO

Booth 40

*P Blakiston's Son & Co, Publishers, Philadelphia*, will exhibit in Space No 40 their publications on Medicine and Allied Sciences, including some English books and translations of some desirable foreign volumes. Special attention is directed to Kaufmann's "Pathology," 3 Volumes, translated by Reimann, Fulkerson "Text-book of Gynecology," Deaver's "Surgical Anatomy," 2nd Edition, Riehl & Von Zumbusch "Atlas of Diseases of the Skin", "Recent Advances Series", Smith "Forensic Medicine," 2nd Edition, Stitt "Tropical Diseases," 5th Edition, Halliburton "Physiology," 18th Edition, Gould's "New Medical Dictionary," 2nd Edition.

## LAMOTTE CHEMICAL PRODUCTS CO

BOOTH 45

LaMotte Blood Chemistry outfits offering simplified blood chemistry methods for the general practitioner as well as the technician will be displayed in a full line at Booth 45. Although the chart on a preceding page does not show this booth, so great has been the demand for exhibit spaces that additional booths have been arranged along the check room foyer, where the LaMotte Chemical Products Company has engaged a prominent location.

At the last annual session of the Southern Medical Association at Asheville, North Carolina, Dr Felix J Underwood (Fellow), State Health Officer for Mississippi, was elected Second Vice President, Dr William R. Bathurst (Fellow), Little Rock, Ark, Chairman of the Board of Trustees, and Dr W S Leathers (Fellow), Nashville, Tenn, Dr Stewart R. Roberts (Fellow), Atlanta, Ga, and Dr Charles C Bass (Fellow), New Orleans, La, were elected members of the Board of Trustees.

Dr V P Sydenstricker (Fellow), Augusta, Georgia, gave a medical clinic and Dr William A Mulherin (Fellow), Augusta, Georgia, gave a pediatric clinic before the Sixth District Medical Society at Macon, Georgia, on November 28.

Dr William R. Dancy (Fellow), Savannah, Georgia, is President-Elect of the Medical Association of Georgia, Dr Allen H Bunce (Fellow), Atlanta, is Secretary-Treasurer.

Dr Morris H Kahn (Fellow), New York City, recently delivered a lecture before the Lackawanna County Medical Society in Scranton, Pa, on the subject "The Industrial Aspects of Heart Disease."

Dr John H Musser (Fellow and President-Elect), New Orleans, addressed the Issaquena-Sharkey-Warren Counties Medical Society at Vicksburg, Mississippi, December 11, on "Throat Infections in General Medicine."

Dr W McKim Marriott (Fellow and Third Vice President), St Louis, addressed the section on Pediatrics of the New York Academy of Medicine, January 3, on "The

Clinical Aspects of the Role of Focal Infections in producing Gastro-intestinal Symptoms in Infants and Children."

Dr Thomas Norton Toomey (Fellow), St Louis, addressed the Lee (Iowa) County Medical Society at Fort Harrison, December 20, on "Pruritus and Dermatitis of Internal Origin."

Dr George B Eusterman (Fellow) Rochester, Minn, spoke before the Rice County (Minnesota) Medical Society at Northfield, November 26, on the subject "Appraisal of New Methods in the Diagnosis of Cholecystic Disease."

Dr John G Ryan (Fellow) of Denver, Colo, has recently become a Life Member through subscription to the Endowment Fund of The American College of Physicians.

Dr H M Eberhard (Associate), Philadelphia, Professor of Gastro-Enterology at Hahnemann Medical College, recently described in detail "The Ionization of Zinc Sulphate in Chronic Colitis" in a clinic at the College.

Dr George B Lake (Associate), Managing Editor of "Clinical Medicine and Surgery," North Chicago, Ill, addressed the Lee County, Iowa, Medical Society, at Fort Madison, December 20, 1928 his subject being "Psychic Factors in Disease."

A small volume of Dr Lake's verses, "An Apostle of Joy," came out in December (Northshore Publishers, Highwood, Ill.), and articles of his appeared in the November "Welfare Magazine," November and December "Medical Economics," November and December "Hospital Topics," and "Prac-

er", and a verse in the November "Step Ladder" He was also reelected editor of *The Bulletin* of the Medical Round Table of Chicago at the annual meeting of that organization

Dr Cyrus W Strickler (Fellow), Atlanta, Ga, addressed the Fulton County Medical Society at Atlanta on December 6 on "Precordial Pain Simulating Angina Pectoris"

Dr Carl J Wiggers (Fellow), Cleveland, December 3, delivered the Chaile Memorial Oration before the Orleans Parish Medical Society at New Orleans

Dr Carl V Vischer (Fellow), Philadelphia, is author of an article in the January 1929 issue of *The Hahnemannian Monthly* entitled "The Management of the Chronic Tuberculous Patient"

Dr Charles W Stone (Fellow), Cleveland, addressed the Eighth District Medical Society at Nelsonville, Ohio, November 1, on "The Modern Trend" Dr Stone is president of the state medical society

Dr E Bates Block (Fellow), Atlanta, delivered an address on "Treat the Mind as Well as the Body" before the Kings County Medical Society, New York, on November 16

Dr Logan Clendening (Fellow), Kansas City, at a meeting of the Jackson County (Mo) Medical Society commemorating the tercentenary of Dr William Harvey's publication of *De Motu Cordis*, November 27, spoke on "The Life and Labor of William Harvey"

Dr Max Emhorn (Fellow), New York, was one of the speakers at the inauguration of the lectures of the International Spanish Speaking Association of Physicians, Dentists and Pharmacists on November 27

Dr Charles W Burr (Fellow), Philadelphia, addressed the section on medical history of the Philadelphia College of Phy-

sicians, December 4, on "Dr Robert Whytt and Internal Hydrocephalus"

Dr James Marr Bisailon (Fellow), Portland, Oregon, addressed the Klickitat-Skamania Counties Medical Society, October 18, at White Salmon, Oregon, on "Mistakes in Diagnosis of Tuberculosis"

Dr Austin B Jones (Fellow), Kansas City, addressed the Clay County (Mo) Medical Society, October 25, on "Diagnosis and Treatment of Cardiac Disorders"

Dr James M Anders (Master), Philadelphia, November 24, spoke before the Association of College Presidents of Pennsylvania, Harrisburg, on "The Research Method of Teaching"

Dr Lawrence Selling (Fellow), Portland, Oregon, read a paper before the Central Willamette Medical Society in November, entitled "Changes in our Views of Neuroses"

Dr Oliver K Kimball (Fellow), Cleveland, addressed the Muskegon County Medical Society at its October meeting on "Prevention of Goiter Among School Children"

Dr William C Rucker (Fellow), New Orleans, was guest of honor at the annual banquet of the Orleans Parish Medical Society in December

Dr John Walker Moore (Fellow), Louisville, has assumed the duties of Dean of the School of Medicine of the University of Louisville, succeeding Dr Stuart Graves (Fellow), who has become Dean of the University of Alabama, School of Medicine, at Tuscaloosa

Dr Cyrus C Sturgis (Fellow), Ann Arbor, spoke before the Shiawassee County (Michigan) Medical Society at its November meeting on heart disease.

Dr Sturgis also addressed the Milwaukee County Medical Society on November 9

Dr James L Bibb (Fellow), Chattanooga,

nooga, has been elected President of the East Tennessee Medical Association for 1929

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Dr Emanuel Libman (Fellow), New York, addressed the Kings County Medical Society, December 18, on "Some Phases of Rheumatic Fever"

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Dr Frank Smithies (Fellow), Chicago, addressed the Marquette-Alger Counties Medical Society, November 3, on "Gastric Hemorrhage, Its Significance and Treatment"

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Dr Gerald B Webb (Fellow), Colorado Springs, will address the medical section of the American Association for the Advancement of Science during its annual session on "The Rôle of Physicians as Poets and Men of Letters"

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Rear Admiral Edward R Stitt (Fellow), Surgeon General of the United States Navy, retired voluntarily at the close of his second full term on November 30. Admiral Stitt was appointed Surgeon General by President Wilson on November 26, 1920, and was re-appointed by President Harding and President Coolidge. He has left Washington for duty as general inspector of activities of the Naval Medical Department on the Pacific Coast and in Hawaii

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A bill has been introduced in the United States Senate by Senator Bruce to authorize Dr William S Thayer (Fellow), Baltimore, "to accept such decorations, orders and medals as have been tendered him by foreign governments." Government authority is necessary before members of the Medical Reserve Corps of the Army can accept foreign decorations

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Dr Robert M Moore (Fellow), Indianapolis, addressed the November meeting of the Ft Wayne County Medical Society on heart disease

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Dr Frederick Epplen (Fellow), Seattle conducted, on November 13, a pathological conference before the Walla Walla Valley

Medical Society. He presented specimens to illustrate obscure ulcerative and malignant conditions

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Dr Arthur F Chace (Fellow), New York, was one of the speakers on January 9 at a testimonial dinner to Dr James McKernon at his retirement as President of the New York Postgraduate Medical School and Hospital

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Dr Edward B Krumbhaar (Fellow), Philadelphia, was recently elected President of the Rush Society of the University of Pennsylvania

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Dr Orlando H Petty (Fellow), Philadelphia, spoke before the Montgomery County (Pa.) Medical Society, November 7, on diabetes

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Dr Warfield T Longcope (Fellow), Baltimore, Professor of Medicine at the Johns Hopkins Medical School, was one of the speakers at the dedicatory exercises, December 5, of the new dispensary and outpatient department of the Johns Hopkins University Medical School

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Dr David Riesman (Fellow), Philadelphia, delivered an illustrated lecture on "Prehistoric Man" before the Brooklyn Institute of Arts and Sciences at the Academy of Music, January 5

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Dr F M Pottenger (Fellow), Monrovia, Calif, presented a paper on "Disturbances in the Vegetative Nervous System in Diseases of the Lungs and Visceral Pleura" before the Association for Research in Nervous and Mental Disease, at its Ninth Annual Meeting, December 27-28, 1928, at the Hotel Commodore, New York City

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Dr Edwin Henes, Jr (Fellow), Milwaukee, is engaged in editing and publishing the Atlanta 1928 Proceedings Volume of the Inter-State Post Graduate Medical Association of North America. This Volume will contain about one hundred articles (clinics and papers) contributed by about seventy of the leading physicians and sur-



geons of America and Europe. Most of the medical contributors, it is reported, are members of The American College of Physicians.

Dr V C Rowland (Fellow), Cleveland, has been elected Vice President of the Academy of Medicine of Cleveland. For a considerable period of time, Dr Rowland has been Editor of the Bulletin of the Academy, and Chairman of the Ohio State Medical Association Committee on Periodic Health Examinations.

Dr Estella G Norman (Fellow), Battle Creek, Michigan, on January 3 was reappointed as a member of the Michigan Board of Registration of Nurses and Trained Attendants by Fred W Green, Governor of the state.

Dr W S Leathers (Fellow), Dean, Vanderbilt University Medical School, Nashville, addressed a meeting at the Rutherford Hospital, Murfreesboro, December 6, on "The Hospital in Relation to the Community."

Dr J Gurney Taylor (Fellow), Milwaukee, was elected President of the Central States Pediatric Society at its recent annual meeting in Pittsburgh.

Secretary Wilbur nominated, on December 26, 1928, Capt Charles E Riggs as Surgeon General of the Navy and Chief of the Bureau of Medicine and Surgery to succeed Rear Admiral Edward R. Stitt (Fellow), who has been transferred to the Pacific Coast to assume charge of the Navy's Medical activities there and in Hawaii. Capt Riggs has been in command of the Naval Hospital at Washington.

Dr E J G Beardsley (Fellow), Phila-

delphia, addressed the first Graduate Fortnight of the New York Academy of Medicine on "Practical Preventive Medicine."

#### GIFTS TO THE COLLEGE LIBRARY

Acknowledgment has been made of the following recent gifts to The College Library.

By Dr F M Pottenger (Fellow), Monrovia, Calif

Book, "Muscle Spasm and Degeneration"

Book, "Tuberculin in Diagnosis and Treatment"

Book, "Tuberculosis and How to Combat It"

Book, "Symptoms of Visceral Disease, 3d edition"

Book, "Clinical Tuberculosis," Vol I, 2d edition

Book, "Clinical Tuberculosis," Vol II, 2d edition

By Dr Raymond J Reitzel (Associate), Galveston, Texas

Reprint, "Lobar Pneumonia in Negroes. The Influence of Syphilis as a Co-existing Disease"

Reprint, "The Effect of pH on the Oxygen Consumption of Tissues"

Reprint, "Parathyroid Extract—Collip as a Diuretic"

Reprint, "Liver Diet in the Treatment of Severe Anemia"

By Dr Philip B Matz (Fellow), U S Veterans Bureau, Washington, D C

Reprint, "Diseases of the Skin Among Ex-Service Men"

Reprint, "The Tuberculosis Problem in the United States Veterans Bureau"

All members are urged to donate copies of their own publications to the College Library, which is intended to be a memorial library and a directory of the publications of our Associates, Fellows and Masters.

## OBITUARY

*Dr Charles Launcelot Minor*

When Charles Launcelot Minor, M D, LL D, specialist in tuberculosis and brilliant writer, died at his home in Biltmore Forest, N C, in his sixty-fourth year Wednesday morning, December 26, 1928, the medical profession and The American College of Physicians lost a member who had achieved national and international fame

Although he had suffered from heart trouble for several years, his death came suddenly. He died at eight o'clock in the morning, a few minutes after he had begun to dress for breakfast

Dr Minor ranks with Trudeau in discovering and disseminating the treatment of tuberculosis. He was generally credited with having been the first physician to realize the importance of the psychological element in the management of tuberculous patients. He was a pioneer in perfecting the method of making physical examinations, which he early considered as important as laboratory tests

After securing his medical degree at the University of Virginia in 1888, Dr Minor was house physician in St Luke's Hospital in New York, 1888-1890. He then went abroad, doing postgraduate work in Berlin, Dublin, London, Paris and Vienna. Returning to this country, he began the general practice of medicine in Washington, D C, but in 1895, having developed tuberculosis, he moved to Asheville which was thereafter his home

In studying his own case, he developed a deep interest in tuberculosis, and, having achieved a rapid recovery, began his career as a specialist in pulmonary diseases. His success was pronounced from the start. His reputation was soon established, and his fame became nation-wide

He was not satisfied with giving his patients the results of his study and genius. He had a veritable passion for educating both the public and the medical profession in the best way to combat what was then called "the Great White Plague"

He wrote on the subject constantly and forcefully. His contribution on "Symptoms and Diagnosis of Tuberculosis" in Klebs' "Tuberculosis," published by D Appleton and Company in 1908, still ranks as one of the greatest pronouncements on the subject in the English tongue

He contributed many articles to both medical and lay journals, all for the purpose of spreading the gospel of the effective treatment of tuberculosis. His brochures on the subject are regarded as classics in medical literature

Dr Minor was also in great demand as a speaker before medical conventions. His eloquence and his thorough knowledge of his subject, combined with his forceful personality, gave him a tremendous acquaintance and popularity among the physicians and surgeons of this and other countries

His eminence and success as a prac-

tioner were paid the tribute of many honors. He was president of the American Climatological and Clinical Association in 1916, president of the National Tuberculosis Association in 1918, president of the Southern Medical Association in 1924. He was a member of the American Medical Association, the Association of American Physicians, and of other medical societies. He was governor for North Carolina of the American College of Physicians.

His constructive ability in his profession was matched by his activities in the life of his home town. He was a member of the Pen and Plate Club, the Civitan Club and the Biltmore Forest Country Club, the Colonnade Club and the chapters of Delta Psi, Alpha Omega Alpha, and the Phi Beta Kappa fraternities at the University of Virginia.

He was a member and vestryman of Trinity Episcopal Church of Asheville. And with the same enthusiasm that he worked for the advancement of his church, he labored for the development and progress of his city.

No better description of Charles Launcelot Minor as a man can be found than the following paragraph from an editorial in "The Asheville Citizen" at the time of his death:

"But it is to his personality that his friends—and all Ashevilleans were his friends—today pay the proudest and most loving tribute. Dr. Minor was a man beloved by his community. His unfailing charm, his flashing wit, his profound and versatile scholarship, his lively interest in all human affairs and his eagerness to be of service to all with whom he came in contact—

these qualities of the man endeared him to our people to a degree of affection that seldom is given to anybody."

In 1926, when Dr. Minor was given the degree of Doctor of Laws by the University of North Carolina, the citation accompanying the award, written by Dr. Archibald Henderson, said:

"Charles Launcelot Minor, Asheville. Born in Brooklyn, N. Y., M. D., of the University of Virginia, later prosecuted detailed researches in medical science in England and on the continent. Through intimate association with the famous Viennese bacteriologist Klebs, to whose renowned book 'Tuberculose' he contributed an important chapter, he early turned the full current of his eclectic mentality upon the complex problems of tuberculosis, its diagnosis, treatment and prevention. Author of many authoritative scientific publications, chiefly devoted to the study of tuberculosis, he ranks today as an authority on that disease without a superior in the entire country. Versatile in attainments, eclectic in taste, like the late Dr. Weir Mitchell, he has, through the magic of his sympathetic and scintillating personality as well as by the depth of his knowledge and the range of his interests, won alike the unquestioned confidence and ardent devotion of his patients. Upon this scientific expert the University will now confer the degree of Doctor of Laws."

Funeral services for Dr. Minor were held the afternoon of December 27, 1928, at Trinity Episcopal Church in Asheville, with the Right Reverend Junius M. Horner, bishop of the diocese,

cese, and the Rev George Floyd Rogers, rector of Trinity, officiating. The body was then taken to New York, where interment was made in Greenwood Cemetery.

Although he received the greater part of his education in Virginia schools and at the University of Virginia, and though he was so thoroughly identified with the South, Dr Minor was born in Brooklyn, N Y, May 10, 1865. His parents were Dr James Monroe Minor of Fredericksburg, Va, and Mrs Ellen J Pierrepont Minor of Brooklyn.

He is survived by his widow, who was Miss Mary McDowell Venable of Charlottesville, Va, and by three children, one of them a son, Dr John Minor, now practising medicine in Washington, D C.

Dr Minor was a great physician and a 'great citizen. He loved men and he loved books. His loyalty to friends and to his community and country was limitless. His career may well serve as a guide to any man who wishes to achieve eminence in his profession and worth to his fellows.

(Furnished by Dr Thompson Frazer (Fellow), Asheville, N C.)

Dr Jacob Wolf (Fellow), Pittsburgh, Pa, died November 19, 1928, at Atlantic City, N J, of cerebral hemorrhage, aged 58.

Dr Wolf was born in Union City, Tenn, educated in Cincinnati where he also graduated from the Medical College of Ohio in 1891. He then spent some time in postgraduate work in Europe and in 1894 came to Pittsburgh where he located on the North Side eventually limiting his practice

to internal medicine. At the time of his death, he was the senior member of the medical staff of the Allegheny General Hospital of Pittsburgh. He had been a Fellow of the College since 1920.

(Furnished by D Lawrence Litchfield, Governor for Penn.)

Dr Eric Kline Bartholomew (Fellow), Chicago, Ill, died December 18, 1929, of epidemic cerebrospinal meningitis contracted from a patient.

Dr Bartholomew received his medical degree from the University of Illinois, Chicago, in 1907. For several years he was assistant clinical professor of medicine at Loyola University School of Medicine, from 1914 to 1918 he was a member of the visiting staff of St Mary's of Nazareth Hospital, and later was a member of the senior medical staff of the same institution. At the time of his death he was also a member of the staff of the Lutheran Memorial Hospital. He was a member of the Chicago Medical Society, the Illinois State Medical Society and a Fellow of the American Medical Association. He was elected to Fellowship in The American College of Physicians April 3, 1922.

Dr Enoch H Miller (Fellow), Liberty, Mo, died October 8, 1928 of influenza and broncho-pneumonia.

Dr Miller was born in 1851, and received his medical degree from the Missouri Medical College, St Louis in 1874. He was a Fellow of the American Medical Association a member of his county and state medical societies, and had been a Fellow of The American College of Physicians since December 27 1924.

## 1929 COLLEGE DUES

The Executive Secretary, Mr E R Loveland, 133-135 S Thirty-sixth Street, Philadelphia, Pa, distributed the bills for 1929 dues at the beginning of January. A great majority of the members have already mailed their checks and have received their 1929 Membership Cards. Several, however, have not to date paid the dues, and are urged to do so immediately. The 1929 Membership Card is necessary to register at the Boston Clinical Session in April, and none but those in good standing will be entered on the subscription list to receive Volume III of *Annals of Internal Medicine*, the new Year Book and other publications. It will assist the Executive Secretary greatly if all dues are paid promptly.

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 THE ADVERTISING SECTION OF  
THIS JOURNAL

Members and Subscribers have noted the addition and successful growth of Advertising in *Annals of Internal Medicine* during the past few months. In April, 1928, The Board of Regents authorized the Executive Secretary to start the promotion of advertising, and appointed an Advertising Censorship Committee consisting of

Dr George Morris Piersol, Chairman

Dr Harlow Brooks

Dr E J G Beardsley

The Committee and the Executive Secretary have worked diligently to build up a high-grade advertising clientele, and seeks to enlist the assistance of every member and subscriber in further promoting this section. The Advertising Section of *Annals of Internal Medicine* is valuable to the College for it helps to defray a part of the cost of publication, it is valuable to the reader because it announces only high

grade products, apparatus and publications, and it must be lucrative to the advertiser to merit his continued patronage. It is known by the publishers that our members and subscribers do patronize our advertisers, but so frequently they do not mention the journal when placing orders or writing inquiries. To patronize our advertisers, to mention *Annals of Internal Medicine*, to recommend our advertising columns, are means of helping The College and of promoting the journal.

*Annals of Internal Medicine*, as the official journal of the American College of Physicians, has a *preferred circulation*, it arrives monthly at the offices of nearly two thousand eminent American internists, diagnosticians, pediatricians, psychiatrists, neurologists, radiologists, pathologists, bacteriologists, medical teachers and investigators, and tuberculosis and public health specialists. Its circulation is *national*, for it goes to every state and possession of the United States, it also goes to subscribers in Canada, Mexico and sixteen other foreign countries. *Annals* has attained, during its seven years of publication, an *eminence in American medicine*, excelled by no other journal devoted exclusively to Internal Medicine. The Advertising Section is limited to twenty pages in one issue, thus giving prominence for each advertisement, and therefore no advertisement is lost in a great host of other advertising. Furthermore, only high grade advertisements are accepted, each tendered advertisement passing review by the Censorship Committee.

Patronize our advertisers and use your influence with other organizations, whose advertising does not already appear in this journal, to adopt *Annals* as a medium for continuous advertising.

# Boston As A Medical Center

By HENRY A CHRISTIAN, M D

THE student of medicine who comes to Boston finds himself with access to modern well equipped hospitals and medical laboratories. There is a wealth of clinical material, freely accessible to graduate and undergraduate medical students. Three excellent medical schools offer a large variety of medical courses. A splendid medical library hospitably invites the reader to use its fine collection of medical books.

In Boston a city rich with traditions of able men and significant events, medicine, too, has its honored traditions. Here was established in 1782 one of the earliest American medical schools, from its inception an integral part of a university. In Boston in 1811 was founded the Massachusetts General Hospital one of our early hospitals, which since its opening in 1821 has never closed its doors to patients. At the Massachusetts General Hospital on October 16 1846 was performed that major surgical operation under ether anaesthesia which more than anything else served to abolish pain from surgical procedures and made possible an ever increasing scope to surgical practice.

Founded in 1782 the Harvard Medical School occupied buildings of Harvard College in Cambridge until 1819 when it was moved to Boston

to secure better clinical opportunities for its students. In 1816, 1847, 1882, and 1906, respectively, special buildings were constructed in Boston for its use. In these a succession of eminent men have labored in the cause of medical education. The Warren family from the days of the battle of Bunker Hill has held a commanding position in Boston. Dr. Joseph Warren played an important rôle in the Revolutionary War. His brother John Warren was Harvard's first professor of Anatomy and Surgery and since 1782, with but a brief interregnum, until last year a Warren has held a professorial chair at Harvard. It was a Warren (John Collins Warren) who performed at the Massachusetts General Hospital that all significant operation under ether anaesthesia given at the hands of W. T. G. Morton. Oliver Wendell Holmes, essayist, poet and professor of Anatomy, gave the name anaesthesia to the process. Holmes' paper on puerperal fever was a very important step in bringing about a general acceptance of the contagiousness of that disease. Benjamin Waterhouse, first professor of the Theory and Practice of Physic, was a Leiden graduate and played an important role in the introduction into America of vaccination against small pox. In July 1800 he vaccinated first of all his

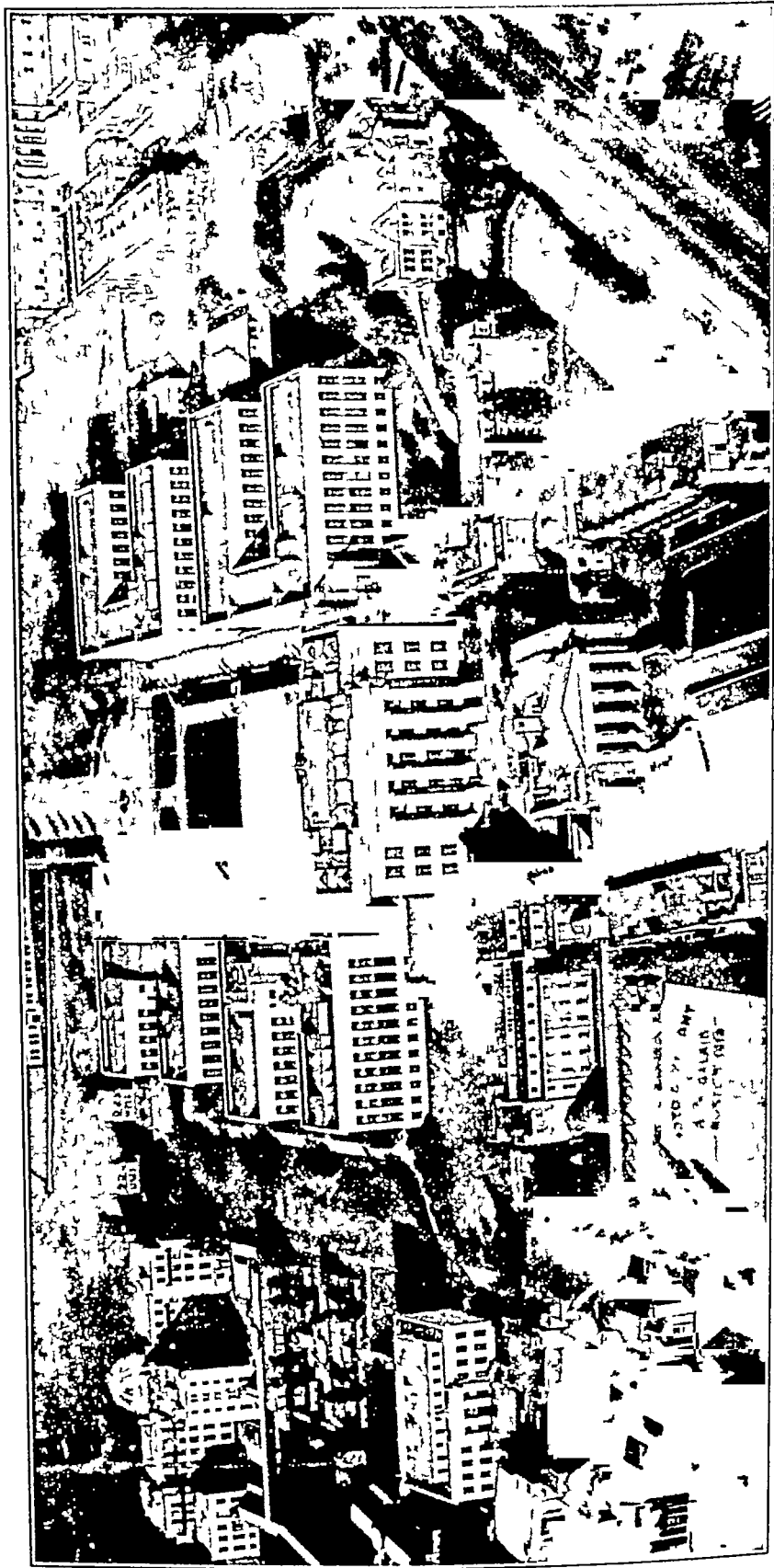


FIG 1 HARVARD MEDICAL SCHOOL, AIR-PLANE VIEW HARVARD MEDICAL SCHOOL, CENTER GROUP OF WHITE BUILDINGS IN FOREGROUND, PART OF PETER BENT BRIGHAM HOSPITAL. AT LEFT, WHITE BUILDING IS HARVARD SCHOOL OF PUBLIC HEALTH BEYOND THIS ON LEFT ARE BUILDINGS OF CHILDREN'S HOSPITAL ON RIGHT IS HUNTINGTON MEMORIAL HOSPITAL AND HARVARD DENTAL SCHOOL



FIG 2 TUFTS COLLEGE MEDICAL SCHOOL

son and later others. At a subsequent date Dr. Waterhouse received from Jenner a silver snuff box containing vaccine inscribed "Edw. Jenner to B. Waterhouse." James Jackson, with Warren, was a founder of the Massachusetts General Hospital and a very outstanding medical man of his time whose "Letters to a Young Physician" are classic. Jacob Bigelow, Harvard's first professor of materia medica, recognized and taught the self-limitation of many infectious diseases. Henry J. Bigelow, a striking figure in surgery, described the Y-ligament and showed its importance in the reduction of dislocations of the hip. David W. Cheever, a remarkable lecturer, taught many students from his store of surgical wisdom. Henry P. Bowditch developed the first laboratory of physiology in this country and in it trained many of the men who subsequently organized departments of physiology in American medical schools. Theobald Smith, professor of Comparative Pathology, demonstrated insect trans-

mission of disease. Reginald Heber Fitz proved that the appendix is the most frequent point of origin of peritonitis and suggested the term "appendicitis," while a colleague, Maurice H. Richardson, spread the gospel of the importance of early operation in appendicitis. Fitz' work on pancreatitis also was of the pioneer type. A son, as Associate Professor of Medicine at Harvard, perpetuates his name in its medical associations. The Shattucks form another family group who have played an important role in Boston medicine. A Shattuck endowed the chair of pathological anatomy at Harvard in 1846; his son and grandson were professors in the departments of Medicine and wise practitioners of their time, teaching both the art and the science of medicine and a great grandson at present serves the school as assistant professor of Tropical Medicine. Richard C. Cabot at the Massachusetts General Hospital originated medical social service work. These and many others in the years



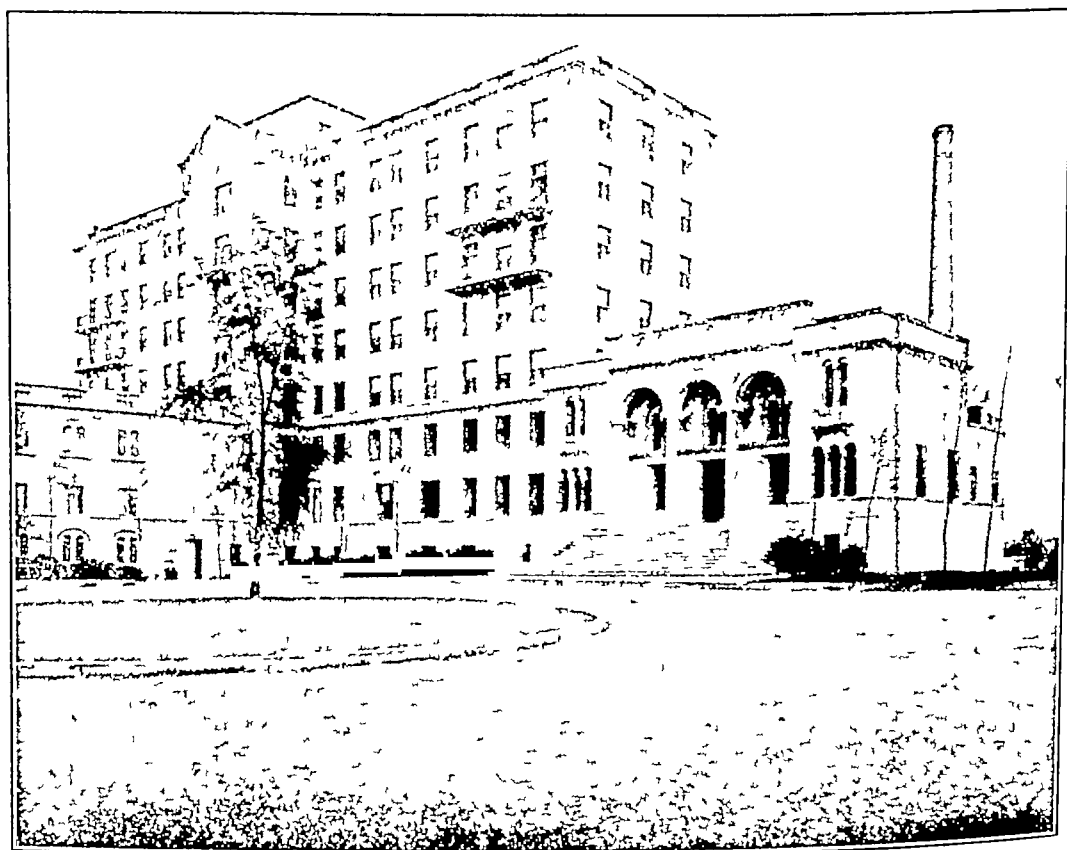


FIG 3 BETH ISRAEL HOSPITAL

since 1782, have built up for Boston truly an inspiring tradition of medicine

Three important medical schools are located in Boston, the Harvard Medical School, (Fig 1), founded in 1782, Boston University School of Medicine founded in 1873 and Tufts College Medical School founded in 1893. The first medical school for women in the United States was founded in Boston in 1848 as the New England Female Medical College. In 1873 this became the Medical Department of Boston University.

In 1927-28 there was an enrollment at Harvard of 521 candidates for the M.D. degree and 439 graduate students at Boston University of 205 candidates for the M.D. degree and at Tufts of 489 candidates for the M.D. degree. The Medical School

budget for the 1927-28 session was as follows, Harvard \$748,870.07, Boston University \$138,000.00, Tufts College \$149,095.18. In addition to the Medical School, Harvard has a school of Public Health with 26 enrolled students and a budget of \$214,309.19 in 1927-28. Both Boston University and Tufts College Medical Schools have building programmes which before many years will give to these institutions greatly improved facilities for medical instruction. The latter plans to move the work of the first two years to Medford where the collegiate department is and there to house the medical students in dormitories.

Boston possesses a large group of hospitals of first rank well equipped for the care of patients and possessed of laboratory facilities making possible

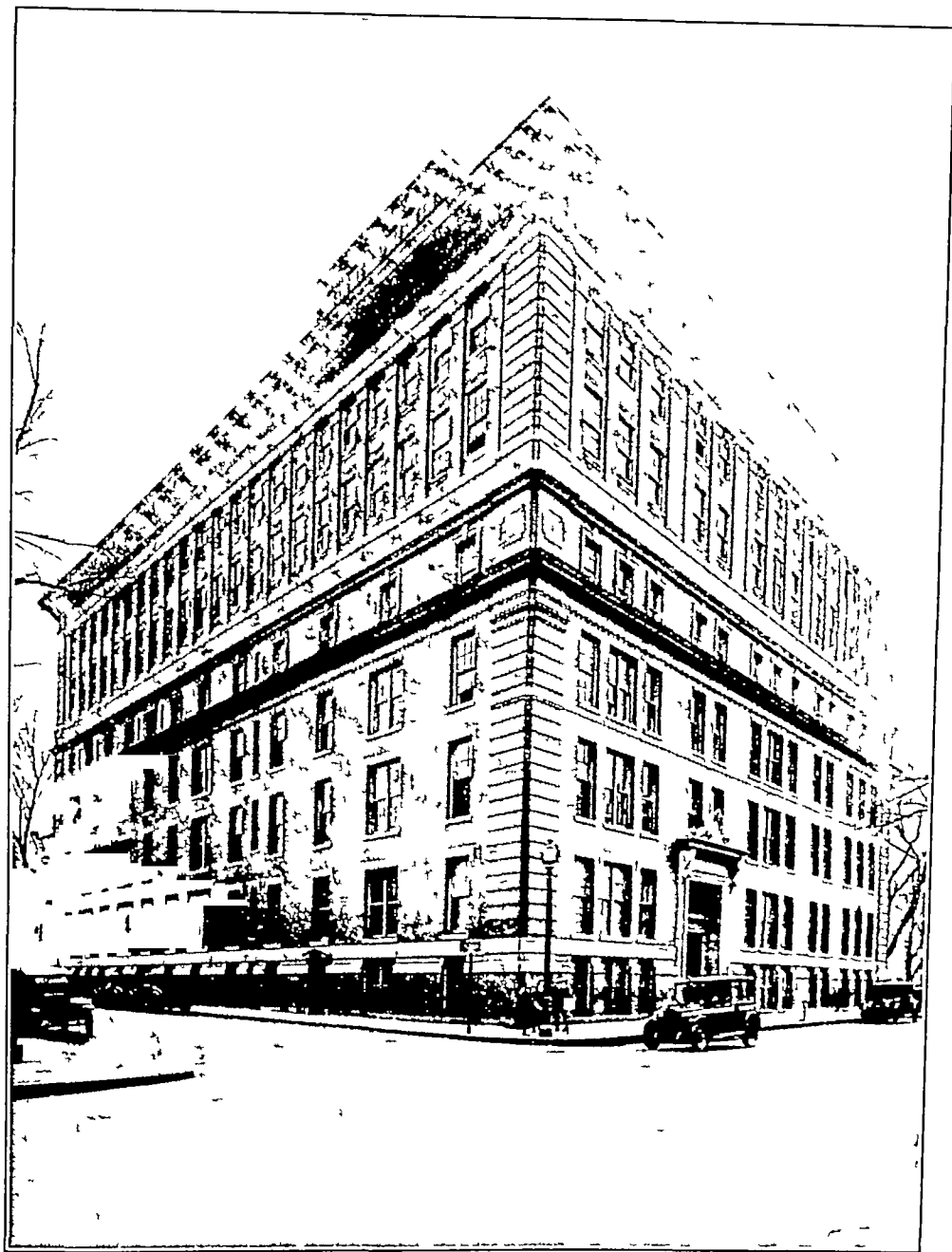


FIG. 4 BOSTON CITY HOSPITAL FRONT VIEW OF THE OUT-PATIENT DEPARTMENT

a wide range of medical investigations. In these hospitals the education of medical students, physicians, and nurses is being carried on throughout the year. These hospitals co-operate with the medical schools in such a generous way that in Boston

there has never been the need for university-owned hospitals. This has brought about for the medical schools an enormous saving in expenditure for clinical facilities and allowed the medical schools to concentrate their resources on the budget for labora-

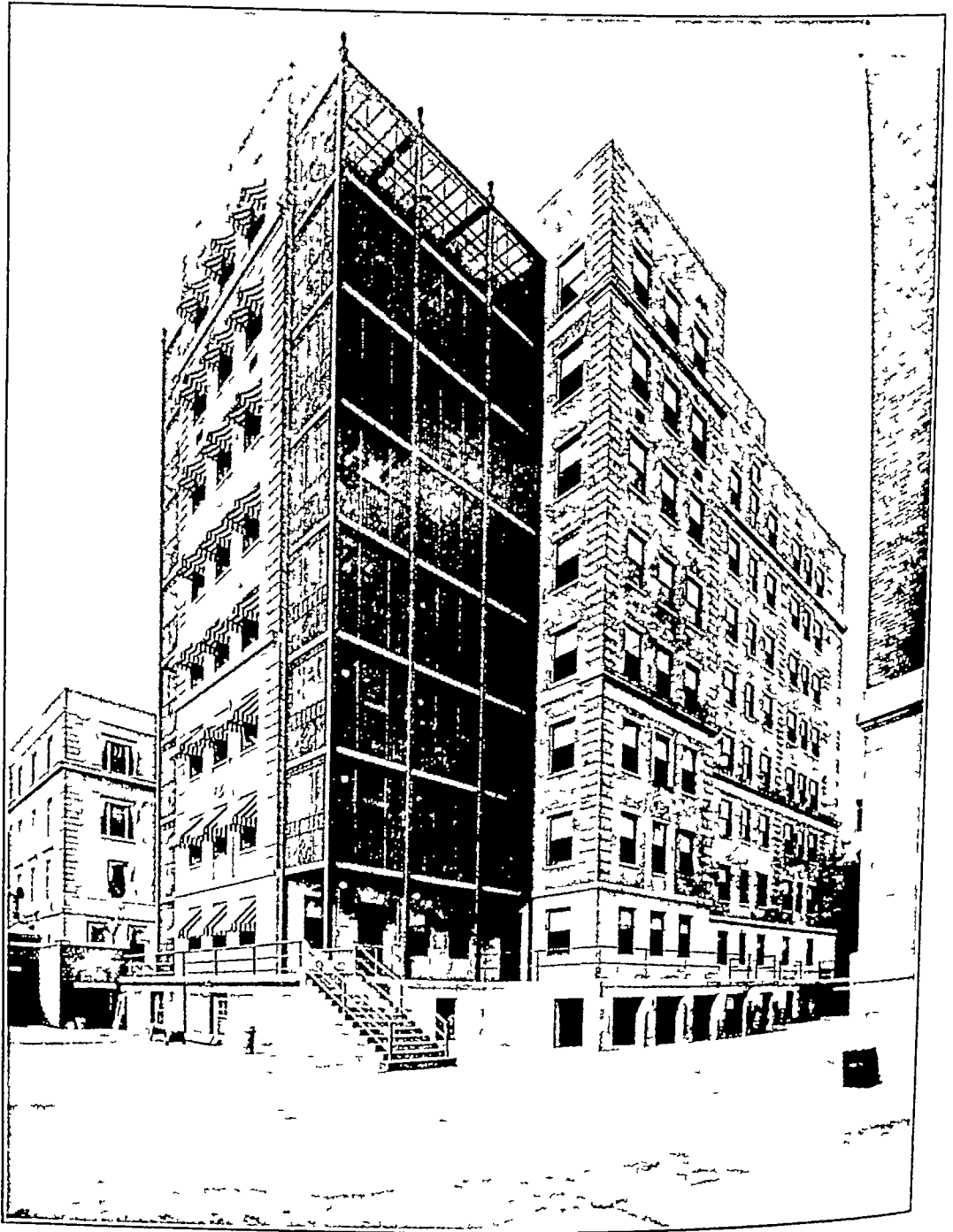


FIG 5 BOSTON CITY HOSPITAL SIDE VIEW OF THE NEW SURGICAL BUILDING

tones, instruction and investigation. Medical schools and hospitals have cooperated in making staff appointments so that the schools have freedom of selection of clinical teachers and the hospitals have profited by having added to their staffs men eminent in their branch of medicine

freely selected from the country at large. Large clinical staffs in the various hospitals greatly reduces the burden of teaching put upon individual members of medical school departments. The spirit of whole hearted cooperation between hospitals and schools in Boston has been a great

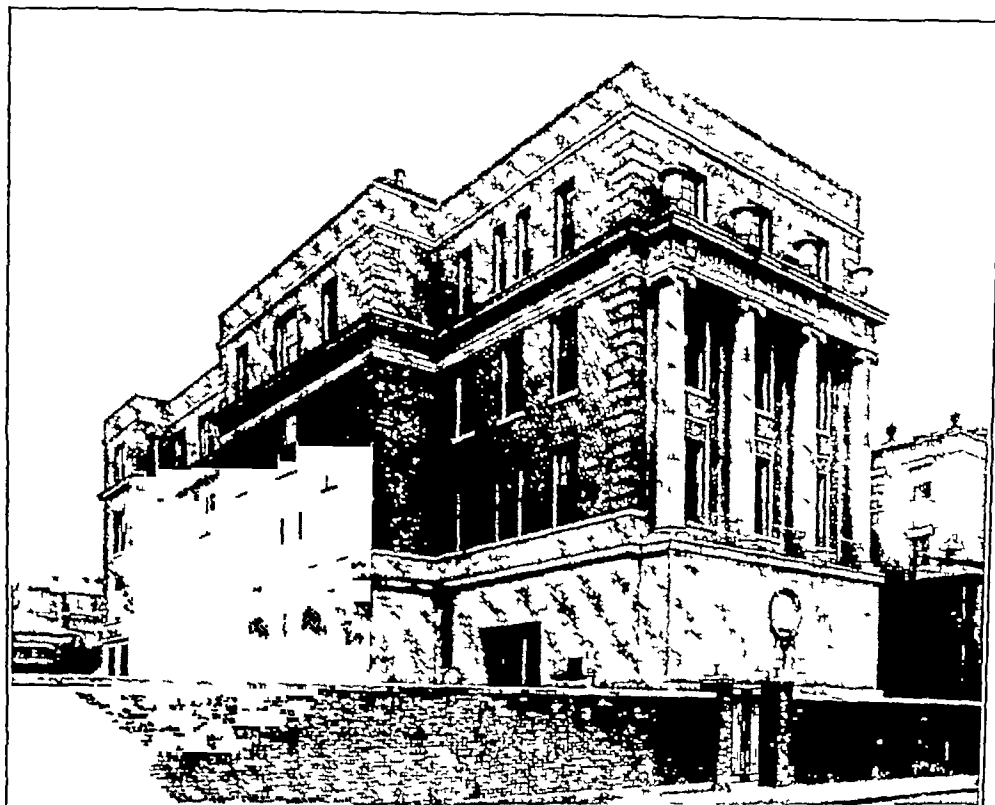


FIG 6 BOSTON CITY HOSPITAL FRONT VIEW OF THE THORNDIKE MEMORIAL LABORATORY

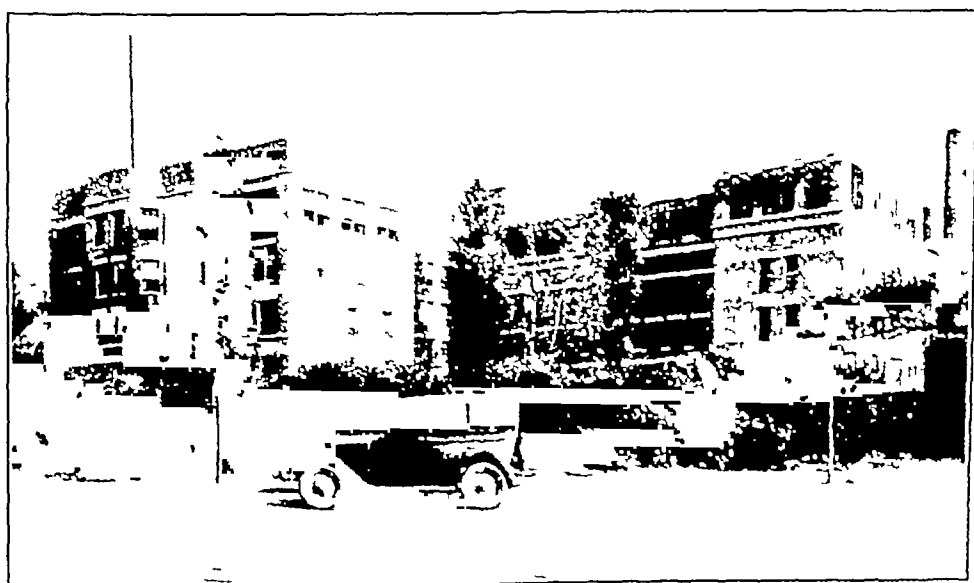


FIG 7 PSYCHOPATHIC HOSPITAL

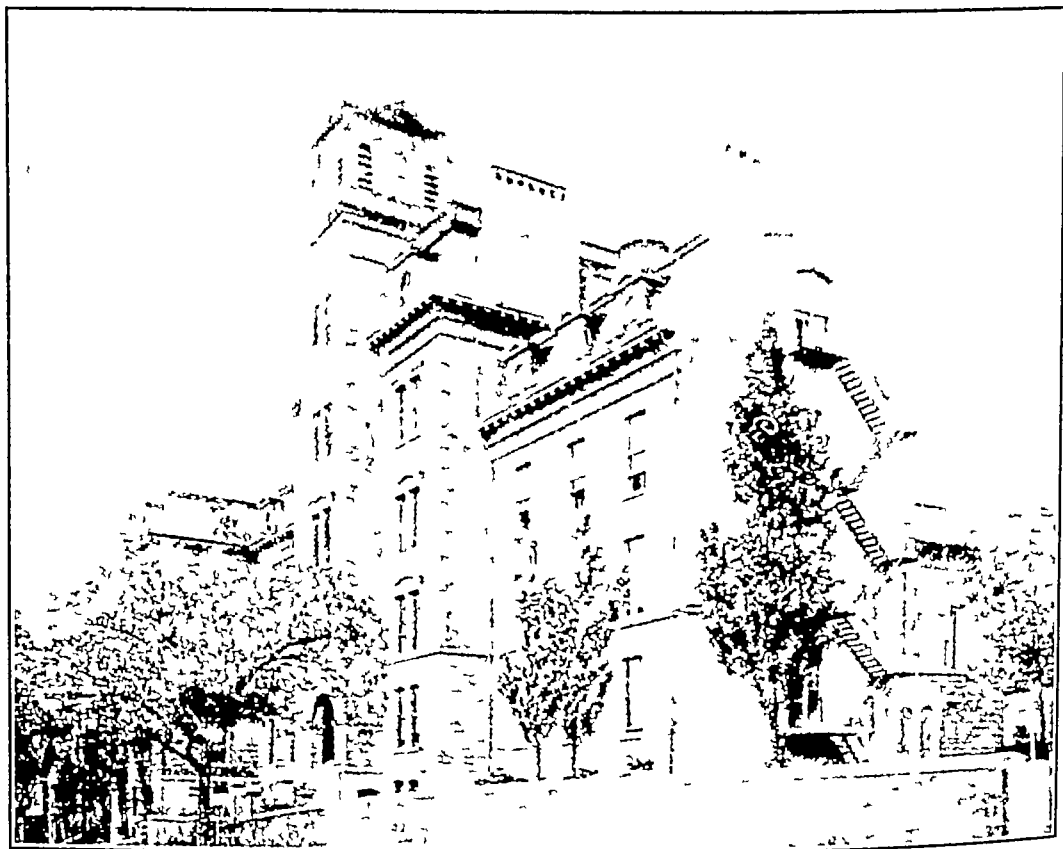


FIG 8 CARNEY HOSPITAL

factor in developing Boston into one of America's leading medical centers

The following brief statements about Boston's larger hospitals will serve to give some idea of the clinical facilities used here in medical teaching

Beth Israel Hospital, (Fig 3), recently constructed at a cost of \$3,000,000, has 180 beds. This is a general hospital with a variety of services

The Boston City Hospital, (Figs 4 and 5), is a general hospital with 1891 beds covering a variety of services. There is also a large Out-Patient Department where last year 81,728 new patients came for treatment. In connection with the hospital the Thorndike Memorial Laboratory, (Fig 6) furnishes extensive facilities for medical investigation. The South Department of the Boston City Hospital cares for contagious diseases and has

a capacity of 338 beds where last year 2,380 cases were treated. Under the Boston City Hospital's direction is a large hospital at Mattapan for the treatment of tuberculous patients with the capacity of 422 beds

The Boston Dispensary maintains a very large Out-Patient Department with 131,231 visits during the past year. In addition there is a well equipped hospital for children with 32 beds chiefly for medical cases

The Boston Lying-in Hospital has 100 beds and during last year treated 2089 patients of whom 1715 were delivered. In addition in the Out-Patient Department 1250 cases were attended

The Boston Psychopathic Hospital (Fig 7) is a state institution for acute, curable, incipient and doubtful cases of mental disease. It has 110

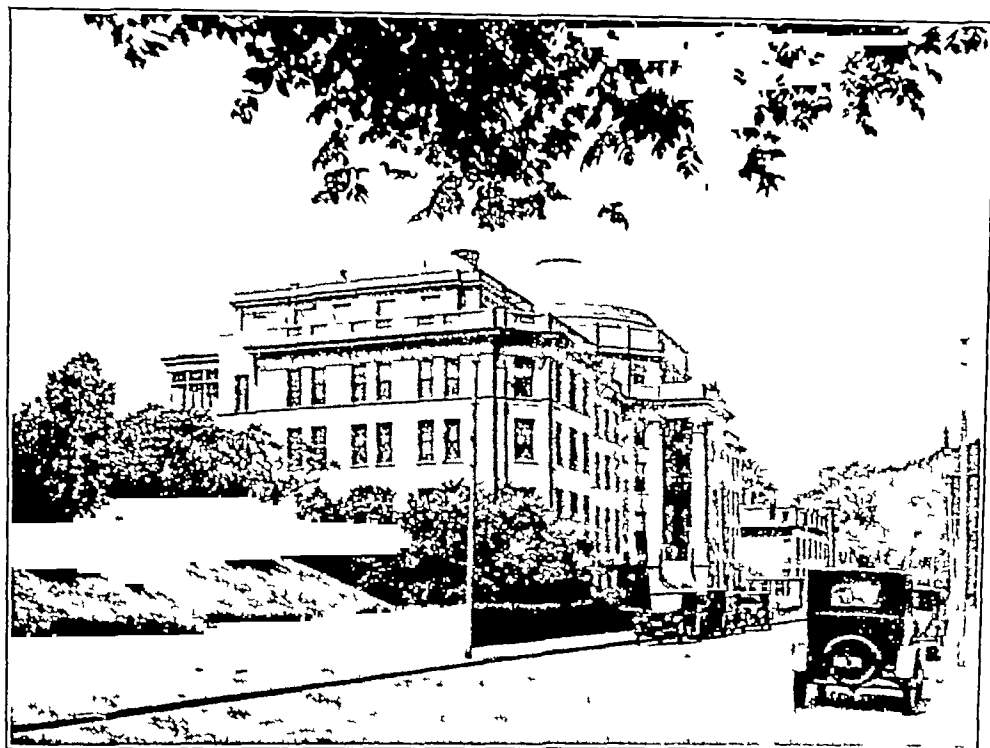


FIG 9 CHILDREN'S HOSPITAL ADMINISTRATION BUILDING

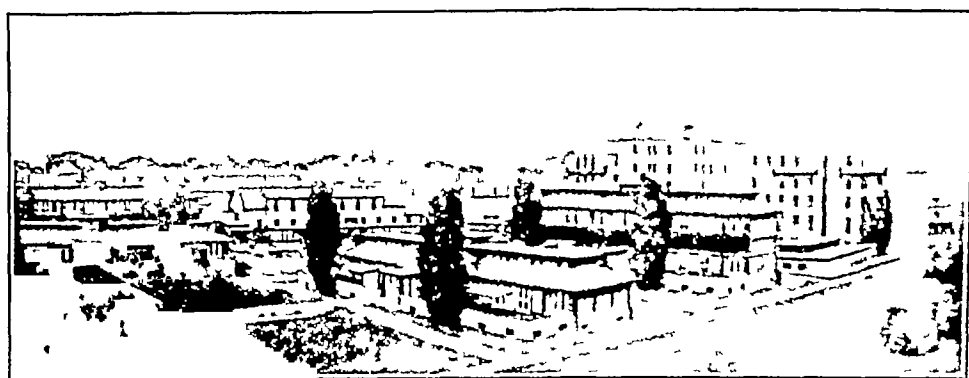


FIG 10 CHILDREN'S HOSPITAL, BIRD'S EYE VIEW

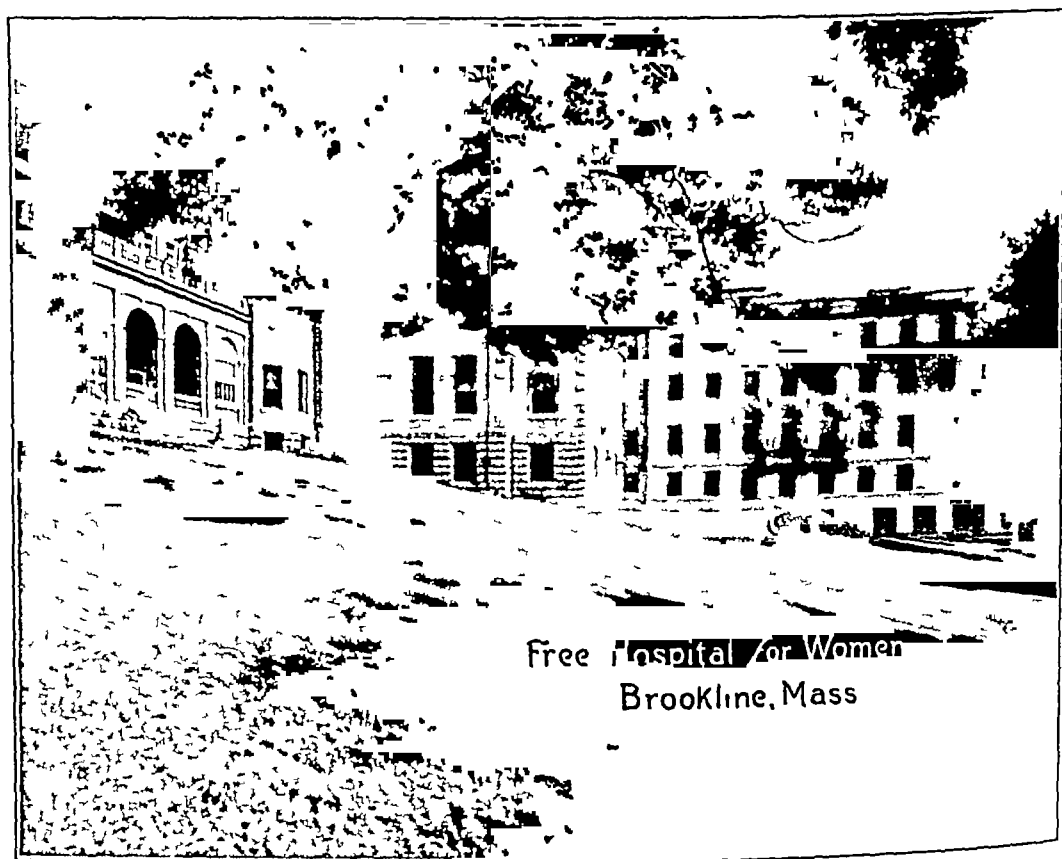


FIG 11 FREE HOSPITAL FOR WOMEN

beds and receives patients at the rate of about 1800 a year. There is also a large Out-Patient Department in connection with the hospital.

The Carney Hospital, (Fig 8), is a general hospital with 220 beds and a large Out-Patient Department.

The Children's Hospital, (Figs 9 and 10), has 244 beds where 5629 cases were treated last year. It has also a large Out-Patient Department in which 57,153 visits were made.

The Free Hospital for Women, (Fig 11), is devoted exclusively to the surgical treatment of diseases peculiar to women. It has a capacity of 94 beds and a large Out-Patient Department.

The House of the Good Samaritan is a chronic hospital for the care of women and children particularly those

with chronic heart disease and cancer. It has 75 beds.

The Infants' Hospital is adjacent to and under the management of the Children's Hospital. It has 66 beds for the care of infants.

Massachusetts Eye and Ear Infirmary, (Fig 12), has 290 beds for the care of patients with diseases of the eye and ear. There is also a large Out-Patient service where in 1927 there were 73,624 visits.

The Massachusetts General Hospital, (Fig 13), has 520 beds for general medical, surgical and pediatric cases, in addition there are special services for skin, orthopedics, laryngology, neurology, etc. Its large Out-Patient Department treated last year 31,871 new patients. The hospital also has extensive laboratories for special

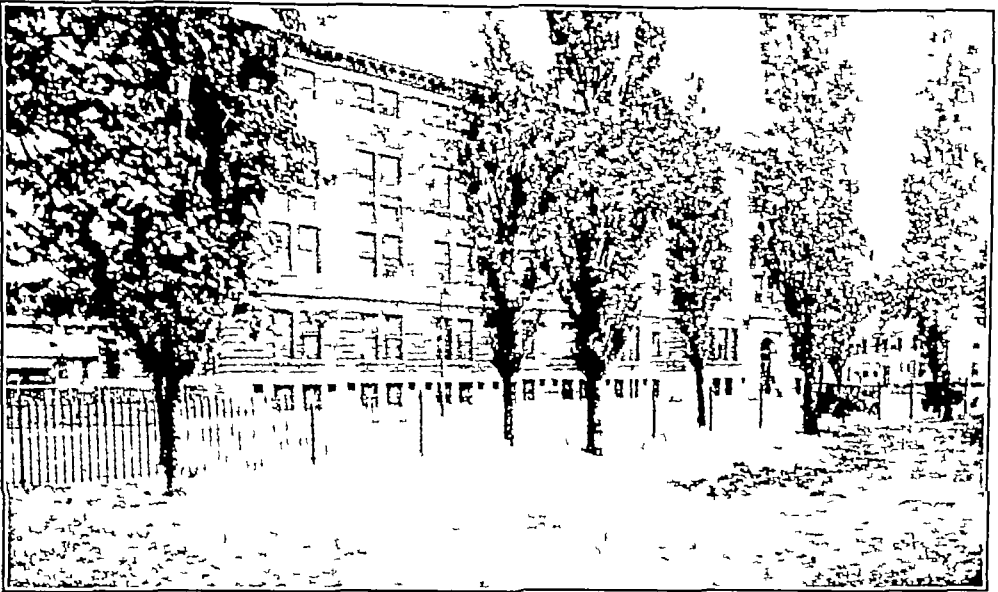


FIG 12 MASSACHUSETTS EYE AND EAR INFIRMARY

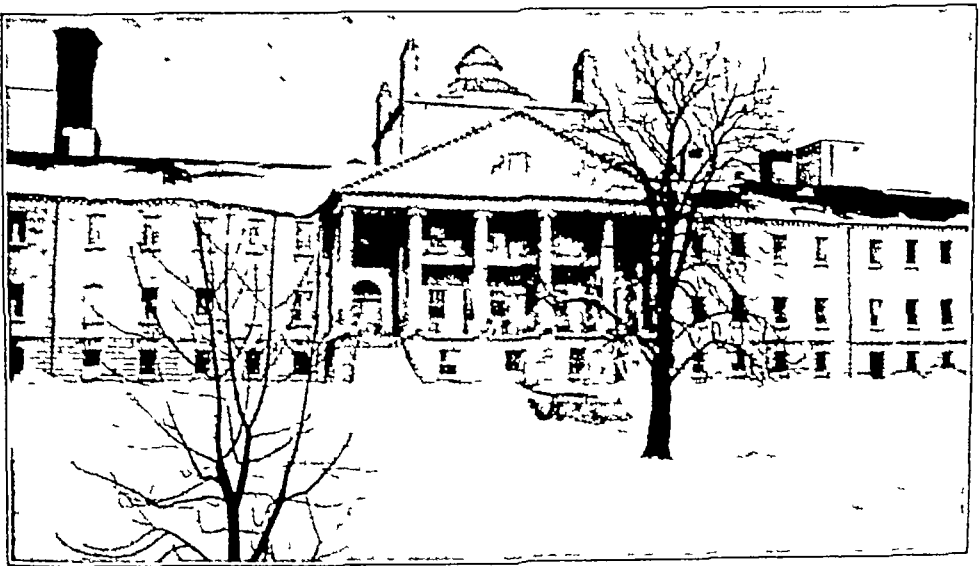


FIG 13 MASSACHUSETTS GENERAL HOSPITAL BULLFINCH BUILDING IN THE DOMT OF WHICH ETHER WAS USED IN MAJOR SURGERY ON OCTOBER 16 1846



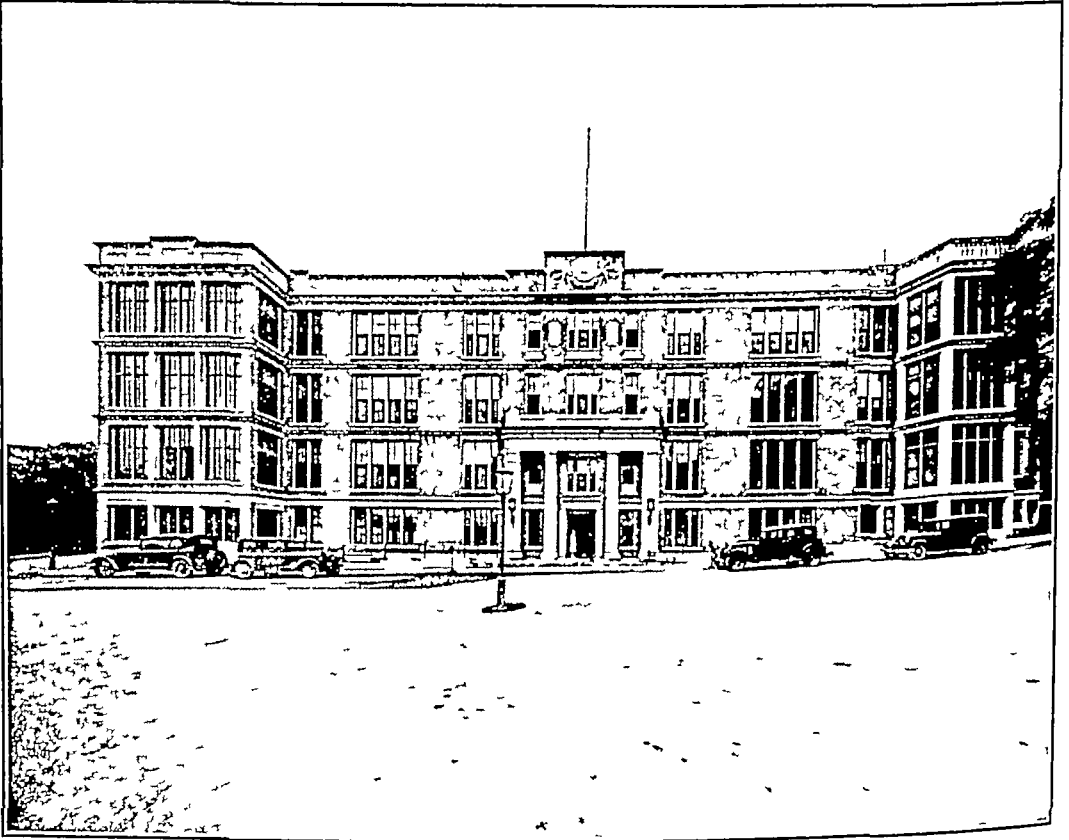


FIG 14 NEW ENGLAND DEACONESS HOSPITAL

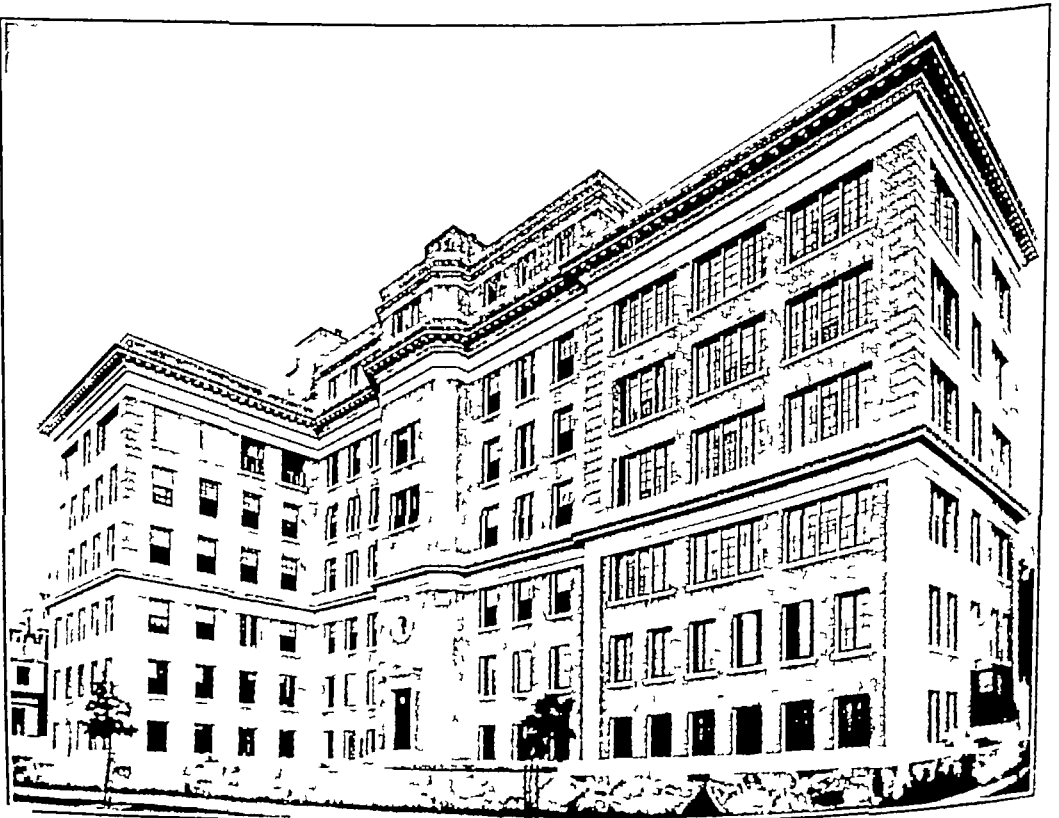


FIG 15 PALMER MEMORIAL HOSPITAL

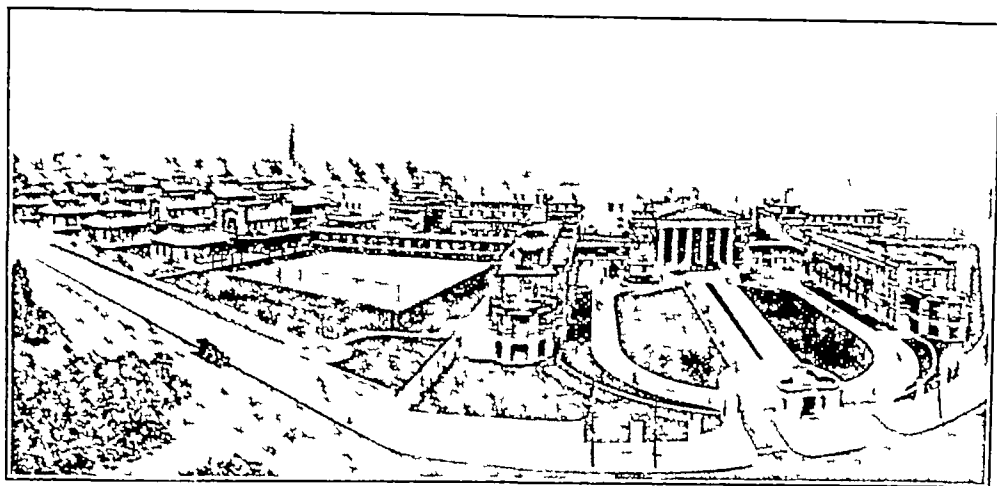


FIG 16 PETER BENT BRIGHAM HOSPITAL

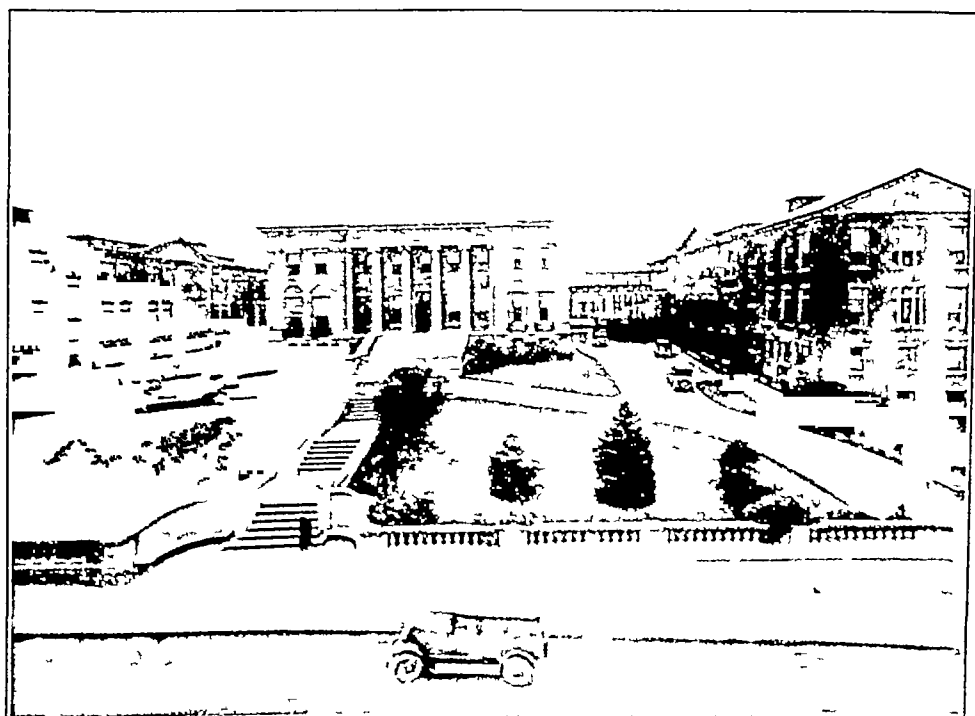


FIG 17 ROBERT BRINK BRIGHAM HOSPITAL

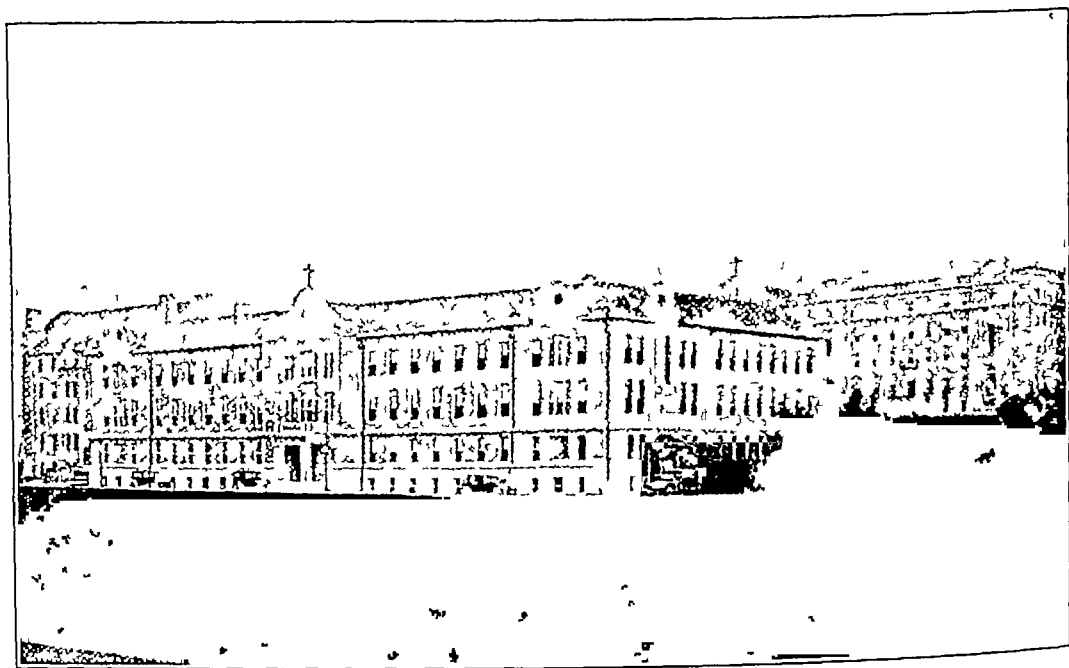


FIG 18 ST ELIZABETH'S HOSPITAL, BRIGHTON, MASS

investigation in addition to those for the routine study of hospital patients

The Massachusetts Homeopathic Hospital is a general hospital with Research, Maternity, Contagious and Out-Patient Departments. In addition, it maintains a small home, Sunnybank, for women convalescents, and assures the responsibility of supplying the Medical and Surgical staff for the Medical Mission Dispensary. It is the teaching hospital of Boston University School of Medicine. 530 beds, exclusive of those in its nurseries, are maintained. During 1927, 11,505 inpatients, of whom 1917 were maternity were cared for and 57,980 visits were made to its Out-Patient Departments.

The New England Deaconess Hospital, (Fig 14), of 181 beds is devoted equally to medicine and surgery. Adjacent to it and under similar management is the Palmer Memorial

Hospital, (Fig 15), of 75 beds for chronic disease especially cancer. During 1927 there were 4,937 patients admitted to the two hospitals. The laboratories are highly developed, and are closely coordinated with those of the Harvard Cancer Commission.

The Peter Bent Brigham Hospital, (Fig 16), has 246 beds for general medical and surgical cases. It also maintains an Out-Door Department open all day long in which in 1927 there were 7699 new cases treated who made 60,671 visits. Besides laboratories for routine work there is extensive provision for medical investigation and laboratories in connection with hospital wards.

The Robert Breck Brigham Hospital, (Fig 17), has 110 beds for the treatment of patients with chronic disease.

St Elizabeth's Hospital (Fig 18), is a general hospital with 245 beds and a large Out-Patient Department.

# An Epidemic of Undulant Fever With a Study of the Associated Milk Supply

By MARIAN E. FARBAR, M.D., *College Physician, Richmond, Indiana*  
and

FRANK P. MATHEWS, D.V.M., *Department of Veterinary Science, Purdue University Agricultural Experiment Station, Lafayette, Indiana*

**B**Y no means a new though as yet, an unsolved problem faces us in the seemingly sudden endemic appearance of undulant fever in this country. It is with the hope of aiding in the solution of its epidemiology and in the meantime to encourage a preventive campaign which would include as one of its objectives the control of the source of the infection that the present outbreak is brought to the attention of the Medical Profession.

The patients and their milk supply were circumscribed on a college campus hence a study of both the patients and the herd was possible. The first two cases appeared early in January 1928, and were diagnosed as "flu", the third with a longer run of fever was suspicious of typhoid fever, and a Widal was conducted but with negative results, the fourth was so typical of remittent malaria that Wright stains were made but no plasmodia were found. The fifth case suggested tularemia on account of the prolonged illness with a high fever, a history of rabbit contact and acute conjunctivitis. Acting upon this suggestion, a specimen of blood was

sent to the Hygienic Laboratory, Washington, D. C., for a serological test, but a diagnosis of undulant fever was rendered by Dr. Edward Francis, whose timely assistance is hereby gratefully acknowledged.

A typical clinical syndrome of undulant fever was observed in twenty-five student patients and one laundress. A dizzy headache, malaise and nervousness marked the onset of the disease and preceded by several days other distressing symptoms such as chills, fever, and a sweating which was frequently profuse. A low pulse rate, 40 to 110, rarely above even with high fever was the rule. There was a mild leukopenia and an anemia present. All but four cases had two or more attacks of fever with apyrexia at intervals ranging from five days to two months. With the exception of these common symptoms the usual wide variety of clinical manifestations which have been observed in other outbreaks were noted. The accompanying fever charts illustrate the several types of the disease which were encountered.

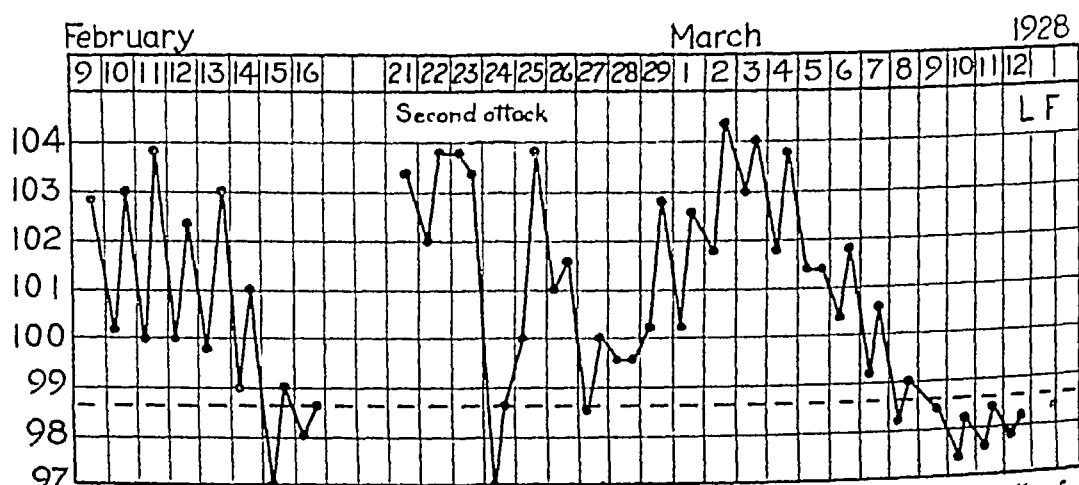


FIG 1—Chart L F From Pennsylvania, a football player This was a chills, fever, and sweating case with no outstanding symptoms otherwise He is now apparently well and back on the squad

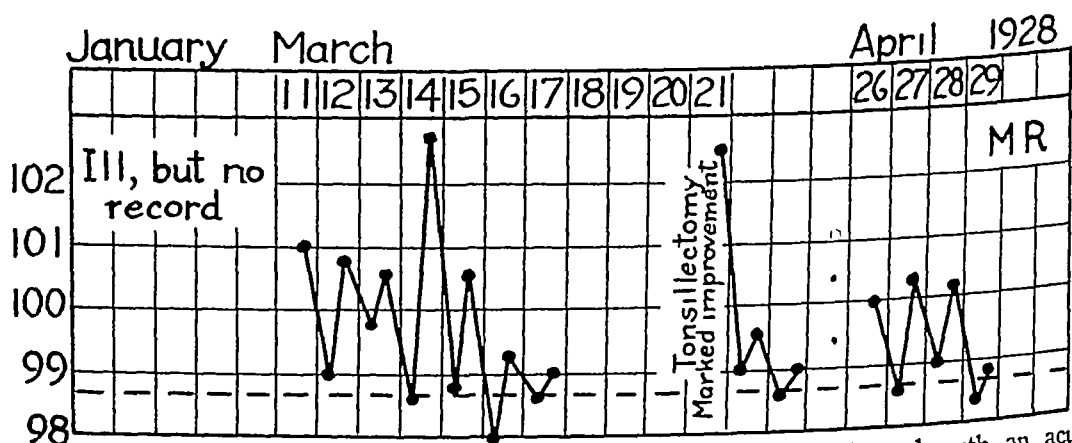


FIG 2—Chart M R From Virginia A severe case, complicated with an acute exacerbation of a chronic tonsillitis, improved rapidly after tonsillectomy

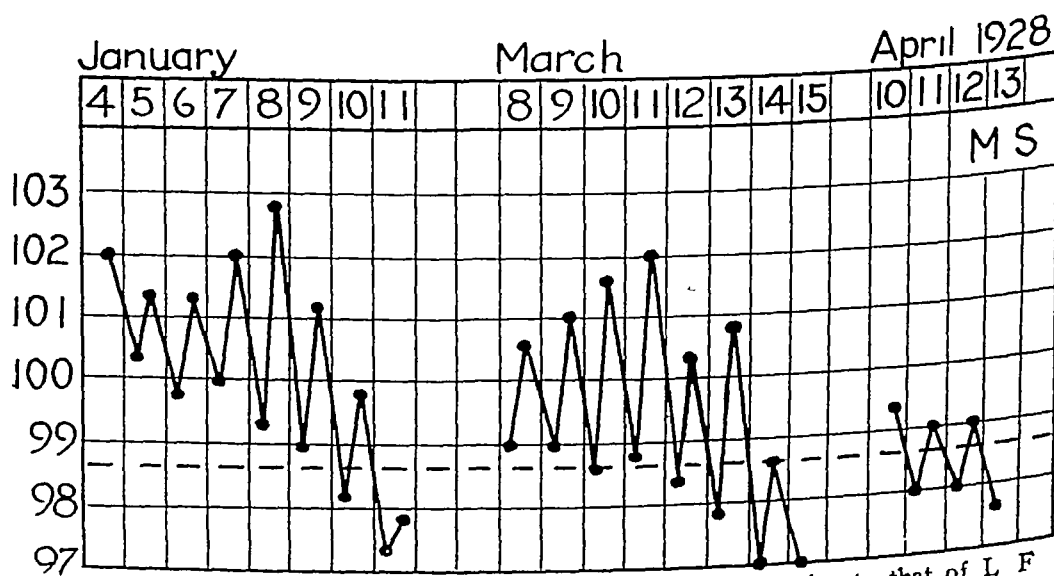


FIG 3—Chart M S From New York State A case similar to that of L F

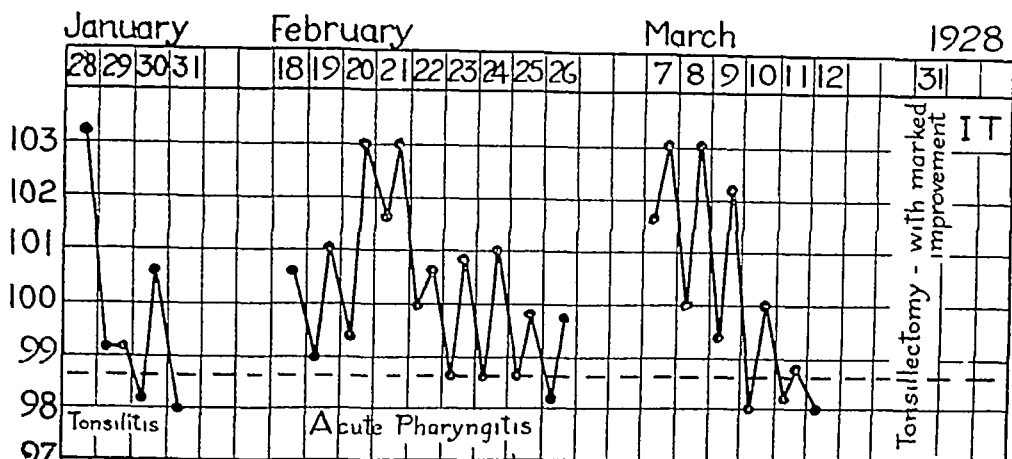


FIG 4—Chart I T A Japanese A case similar to that of M R These and several similar cases suggest chronic infected tonsils as a factor in predisposing etiology

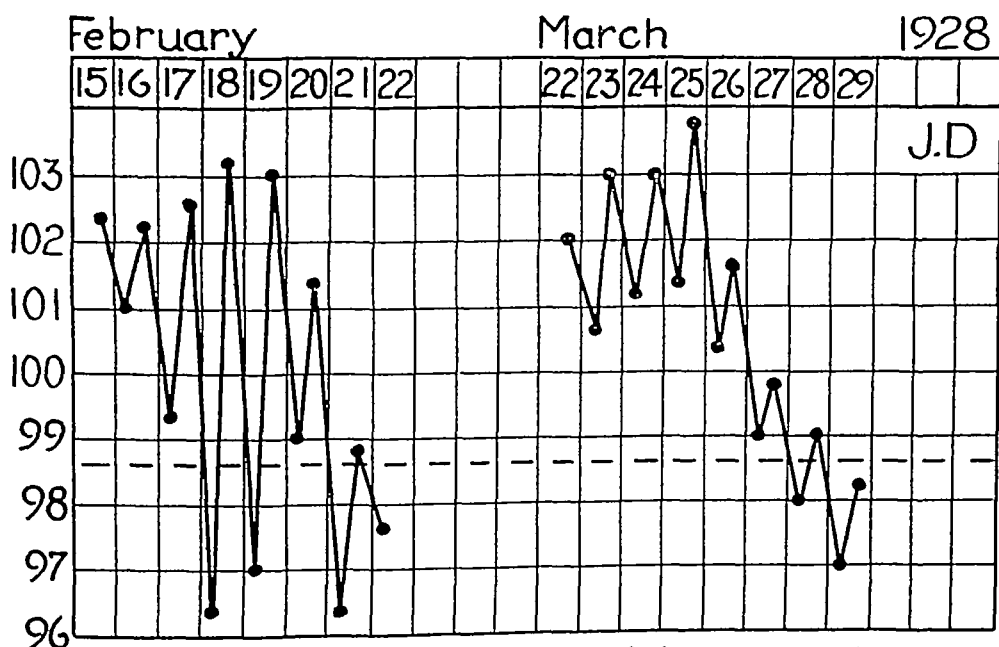


FIG 5—Chart J D From Indiana A case of the remittent malaria type, the fever would remit each afternoon with a severe chill, preceding and a heavy perspiration following The patient was quite ill but has apparently recovered at this writing

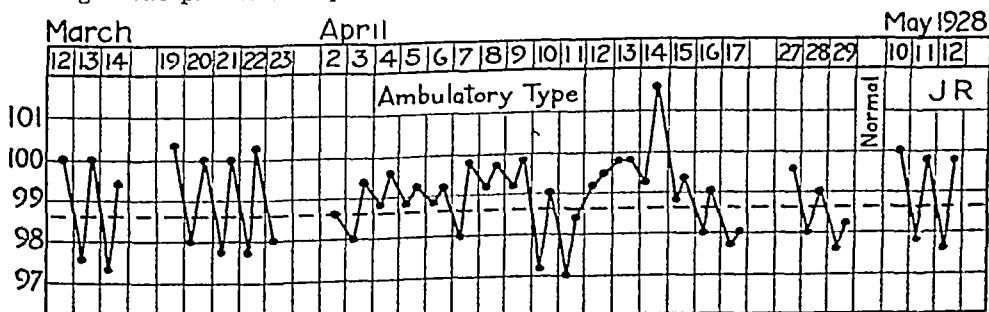


FIG 6—Chart J R From Indiana This was an ambulatory type of the disease. This and two other cases continue to have undulations of fever every two or three weeks with sweating, chills and nervousness

Of the twenty-six cases which were recognized clinically, fourteen gave positive reactions to the agglutination test for undulant fever, six were negative (one test only) and blood was not sent in from the remaining six. The macroscopic agglutination test was employed throughout. Dr. Francis used the three antigens, Br. abortus, Br. melitensis and B. tularensis. The junior author employed but the one antigen, Br. abortus. The agglutinin titres of the fourteen positive cases are given in Table I. It is of interest to note that the titres in fifty per cent of the tests were higher for Br. abortus than they were for Br. melitensis. Cross agglutination for B. tularensis was slight, but observed in five cases.

In addition to the serological tests, the blood samples from the suspected cases were subjected to bacteriological examinations. Portions of the blood

clots and the serum not used for the serological tests were introduced into recently boiled bouillon and incubated under aerobic conditions and in jars in which approximately ten per cent of the atmosphere had been replaced with CO<sub>2</sub>. For a period of one week daily transfers were made from the bouillon to agar slants but Br. abortus was never isolated. The remainder of each blood clot was macerated in sterile salt solution and injected into guinea pigs. The guinea pigs were killed six to eight weeks later and were examined for the lesions, and the presence of Br. abortus but with negative results in all cases. The blood of the guinea pigs never reacted to the agglutination test for infectious abortion.

The status of the dairy herd from which the entire milk supply was obtained was as follows. Twenty-three cows seven of which gave positive re-

TABLE I.—AGGLUTININ TITRES OF FOURTEEN CASES OF UNDULANT FEVER

Case No	Initials	Sex	Age	Date tested 1928	Brucella abortus No 456	Brucella Melitensis No 428	Bacterium Tularensis	Treatment of Serum
1	L F	M	22	Mar 24	1280	320	80	56° C ½ hr
2	M R	F	19	"	1280	1280	20	" "
3	M S	M	19	"	2560	1280	0	" "
4	I T	M		"	640	640	40	" "
5	J D	M	24	"	2560	640	160	" "
6	J R	M		"	160	80	0	" "
7	D W	M	18	Apr 7	640	640	0	" "
8	A C	F	19	" 13	320	160	0	" "
9	O R	M	25	" 14	640	640	0	" "
10	W O	M	21	" 16	2560	1280	80	Unheated no preservative
11	E J	F	21	" 20	160	80	0	" "
12	S R	F	17	" 20	160	160	0	" "
13	M. C	F		" 21	320	320	0	" "
*14	A M	F	47	May '22	100			

\*Tested by the junior author, the other thirteen cases were tested by Dr. Francis

actions to the agglutination test for infectious abortion. Br abortus was isolated from the milk of three reactors, two of which were found to have advanced cases of mastitis. The udder of a third, reacting cow was likewise affected, although Br abortus was not isolated from the milk of this animal. The cows had never been in contact with goats, and there were no hogs maintained upon the premises for breeding purposes. Adjacent to the cow lot was a pen of feeder pigs which had been placed in the feed lot as young pigs and were not of breeding age when the outbreak of undulant fever occurred.

About two months after the dairy herd was examined and corrective measures established, six of the gilts were isolated from the remainder of the pigs in the feed lot. The milk from the mastitis cases was then fed to the six gilts for a period of two weeks. (Bacteriological examination showed that two of the cows were still eliminating Br abortus in the milk.) Immediately following the feeding period four of the gilts were bred. The six animals have been repeatedly tested with the agglutination test for infectious abortion, but with negative results to date. One of the gilts had evidently conceived before the male pigs in the feed lot were castrated since this animal gave birth to seven live pigs, nine weeks after she was segregated with the other five gilts. The pigs were killed as soon as they were farrowed and their organs examined for the presence of Br abortus but with negative results. Negative results were likewise obtained with the fetal membranes.

#### DISCUSSION

Since there was no history of contact with goats or aborting hogs, it is quite improbable that these animals had any direct connection with the present outbreak of undulant fever. That the infected dairy herd was directly responsible was supported by several important facts, first, the demonstration of Br abortus in the milk, second, all the undulant fever cases were heavy consumers of raw milk, with two exceptions, and in these two cases cream was consumed with cereals, third, since pasteurization of milk was established no new cases have developed, fourth, the sudden outbreak among students which had assembled from a wide range of territory indicated that the infection was acquired locally and not imported.

A point of interest in the present observations is the number of clinical cases which failed to react to the agglutination test. Similar observations have been made by other investigators and serve to illustrate the fact that a single negative agglutination test is insufficient evidence to exclude undulant fever in the face of a typical clinical syndrome of the disease. It would have been of scientific interest to have been able to isolate Br abortus from the blood-stream of some of these patients but since this was not accomplished, the results should be interpreted as an absence of bacteremia and not as the absence of Br abortus as the etiological factor.

The tendency of some investigators to consider swine as the reservoir of infection is not supported by the present observations. The failure to



infect gilts by feeding milk which was shown to contain *B abortus* must be considered as evidence that the organism concerned in this instance was not the porcine type. Furthermore, the cultures of *Br abortus* which were

isolated from the milk have been found by both the junior author and Dr I F Huddleson,\* to be of bovine type.

\*Personal communication



# Report of a Case of Primary Multiple Myeloma With Bence-Jones Protein in the Pleural Effusion

By EUGENE E. MARCOVICI, M.D., F.A.C.P., *New York City*

**J.** H. CORIAT in 1903 described for the first time the occurrence of Bence Jones protein in the pleuritic effusion of a patient suffering from Korsakoff's psychosis, with extreme tenderness of the ribs and no albumosuria.

The case I wish to report has been under my observation from Dec. 13th, 1927, till to its exitus on April 13th, 1928. The history presents the following data: Mrs. Th. B., 55 y. old, born in Fubine, Italy. Mother died at the age of 40 due to some form of anemia. Father died at the age of 70, after apoplexy. One sister 60, a brother 65, both well. Patient menstruated at the age of 14, married at 18, had six children, all well. Her husband died at the age of 40 from Bright's disease.

Patient's normal weight was about 100 lbs, had worked very hard and was poorly nourished. Outside of constipation, the patient did not remember any serious ailment.

In February 1927, the patient felt neuralgia-like pains over the left side of the chest, most of the ribs were sensitive at the slightest pressure. No fever, appetite poor.

In April she went to the farm of her brother in Connecticut for a rest, while carrying a pail of water, she felt a sudden pain in the left side of the chest, similar to the breaking of some ribs. In August 1927 the patient came back to the city. The pains were rather increased, severe shooting pains in most of the ribs, on the left side and over the heart region. No appe-

tite, always constipated. Loss of weight of about 12 lbs, sleep very poor.

In October 1927, the patient had X-rays taken of her chest, report not known to the family. In November at the Reconstruction Hospital, where I saw the patient in consultation, they were of the opinion that primary carcinoma of the cecum was the probable diagnosis and that the rib conditions were carcinoma metastases. I found then no signs of malignancy in the intestinal tract.

On December 13th the family brought the patient to my office for another examination and further treatment.

She complained of severe pains in the left side of the chest, poor sleep on account of the pain, sometimes night sweats, seldom cough. Walking was difficult, weakness, lack of appetite, gradual loss of weight, constipation, no nausea. Shortness of breath, sporadic pains, redness and slight swelling of the right toe and the right trochanter. Headaches mostly forehead, no dizziness. Paresthesia in both forearms. Pt. was pale, prematurely aged, and poorly nourished, weight 89 lbs, Temp 99.6° Resp 36, Pulse tachycard. 104, Blood pressure 110/80. Dyspnea. Blood examination: E. 4475000, L. 13150, Hemoglobin 85%, Differential leucocyte count: P 72, L 31, E 2, Ba 2, n Mye 10. Urine examination: Albumin in traces, Sugar neg, Bence Jones protein neg, Sediment no casts, few epithelial cells and WBC. The head was carried inclined toward the left, the muscles of the neck were contracted (not a recent condition), possibly following

a rheumatic myositis The face was wrinkled, pale, emaciated Panniculus adiposus was absent The head nerves were normal The tongue was not coated, slightly dry The neck organs were normal Pharynx and larynx did not show any peculiarities No gland enlargements, the veins were not distended The chest looked very narrow, the breathing appeared superficial and frequent

The lower intercostal spaces showed retraction during inspiration, the right side of the thorax expanding less than the left, basal adhesion left, dulness over the right lower lobe. Both apices retracted There was vesicular breathing over the apices, no râles, over the right base were friction sounds, over the left lower lobe reduced breathing sounds, no râles or friction

The fluoroscopic examination of the chest, showed that several ribs have undergone a destructive process, especially the fifth right rib and the third, fourth and fifth left rib The right hilus showed a great amount of infiltration, in the shape of an interlobar effusion The right base showed adhesions The heart of normal size, the sounds clear, the pulse rhythmical, equal but rapid

The examination and palpation of the abdomen did not show any pathology The diagnosis made at my office was multiple myeloma of the ribs and advised that the patient be placed in the hospital for observation

The patient has been under very careful observation The temperature had been normal up to the time of her admission, when it reached 101.6 F Upon examination I found an accumulation of right pleural effusion The X-ray examination by Dr Pound on January 9 reports the following findings Films were made of the skull, forearms, femurs, legs and feet There was no evidence of any pathological changes in the bones or the periosteum Films of the colon after a barium enema showed no evidence of cancer or obstructive loops or kinks Film of the chest showed the lower half or two thirds of the right chest filled with a pleural effusion The fifth left rib showed complete destruction of all of the bony portion except the extreme anterior end The

sixth rib left posterior axillary line showed a destruction for a distance of a trifle over an inch The seventh rib posteriorly showed several small punched-out areas The tenth rib left showed destruction of the posterior two thirds There were a few areas of pleural involvement in the left chest (Fig 1) Diagnosis Multiple myeloma

On January 9, the temp was 101.6 F The urine was negative for Bence Jones, the blood count findings were as follows: E 450,000 L 15100 Hem 100%, P 85, L 12, E 1 The pleural effusion reached the spina scapulae The fluid obtained through paracentesis had a specific gravity of 1024, the reaction for Bence Jones protein was doubtful (Wells, Chem Path., W B Saunders Phila 1925, p 597) The X-ray report (Dr Pound) on the day after the paracentesis, Jan 10, read Pleural effusion has been removed through tapping Considerable amount of fluid has been removed The sixth rib on the right side in the axillary line showed a destruction for a distance of an inch and a half (Fig 2, Fig 2a)

The blood count on Jan 10th was L 15000 P 81, L 5, E 1, 17, Ba 2, n Myel 4

On Jan 11th L 10,000, P 77½%, L 6, 1 7½%, Mo 1, Trans 0.5%, E 1, Ba 1%, Myel 1½%

On Jan 14th the temp was 99.9°, the leukocyte count 8200, P 73, L 12, 1 3, Mo 2, E 4, Ba 2, Mve 4

On Jan 18th, leukocyte count was 8000 P 68, L 7, 1 8, Mo 7, Trans 3, E 15½%, Ba 15%, Myel 2

On Jan 21st, L 10,000, P 73, L 11, 1 5, Mo 4, E 4, Ba 1, Myel 2 The fluid in the chest had collected again The X-ray report as follows Effusion in the right chest has reaccumulated There appeared to be a number of punched-out areas in several of the ribs, which showed no previous involvement The sixth rib showed further destruction in the posterior portion (Fig 3)

On Feb 8th the X-ray report reads Pleural effusion filling most of the right chest, several small areas of pleural thickening (Fig 4) Blood report Hem 80%, L 5,000,000, L 8000, P 69, 1 1, 1 25 Mo 2, E 2

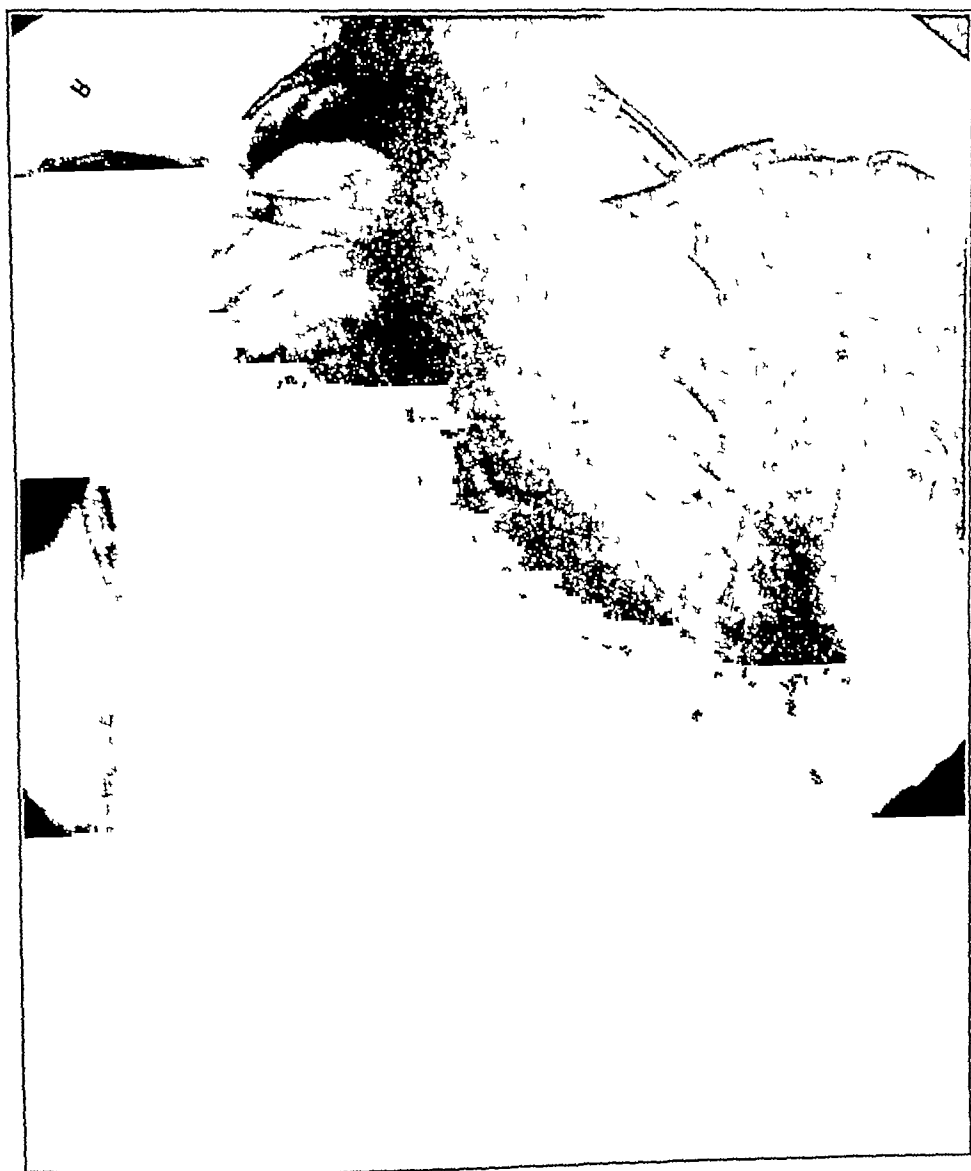


FIG 1

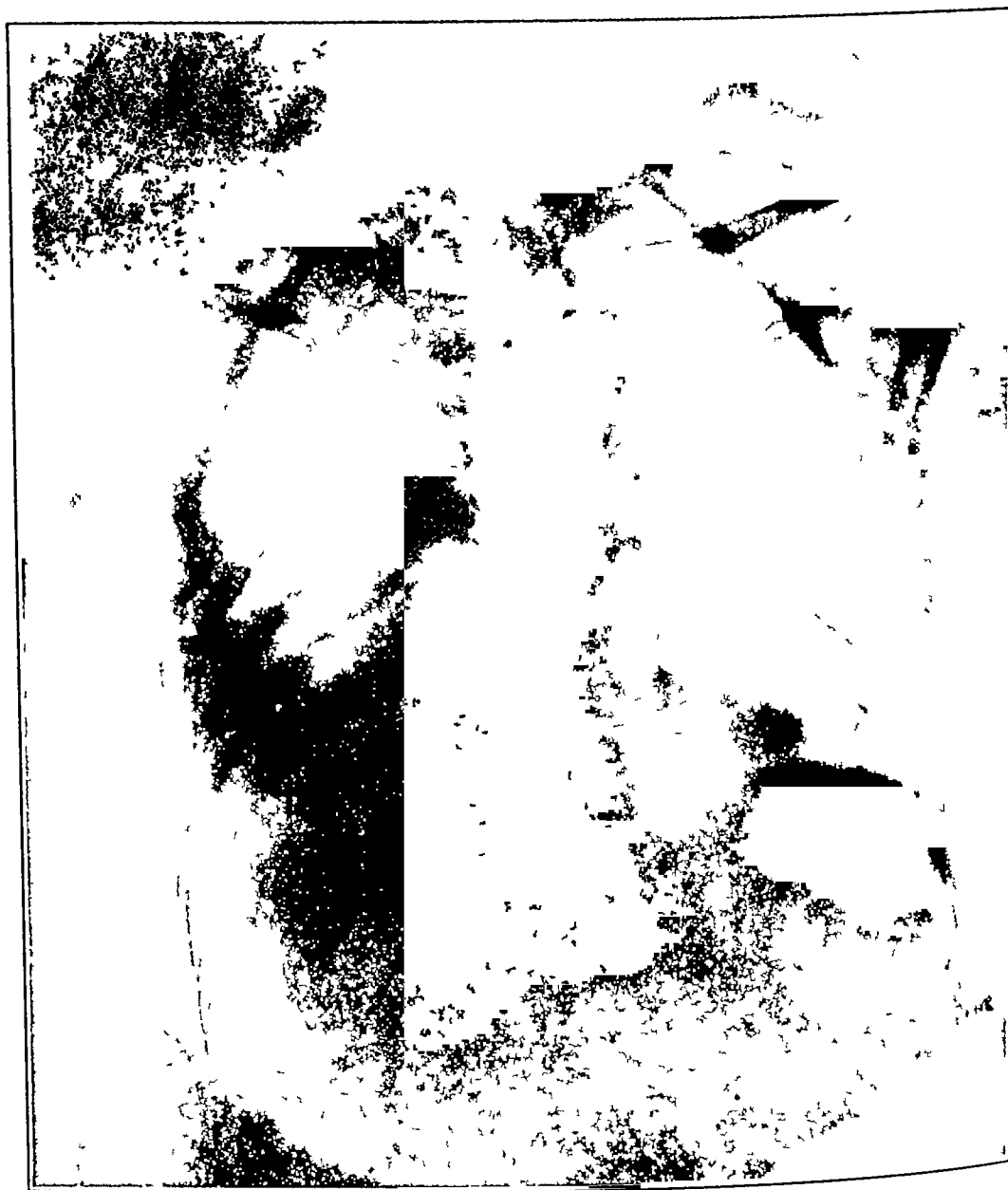


FIG 2



FIG 2a



FIG 3

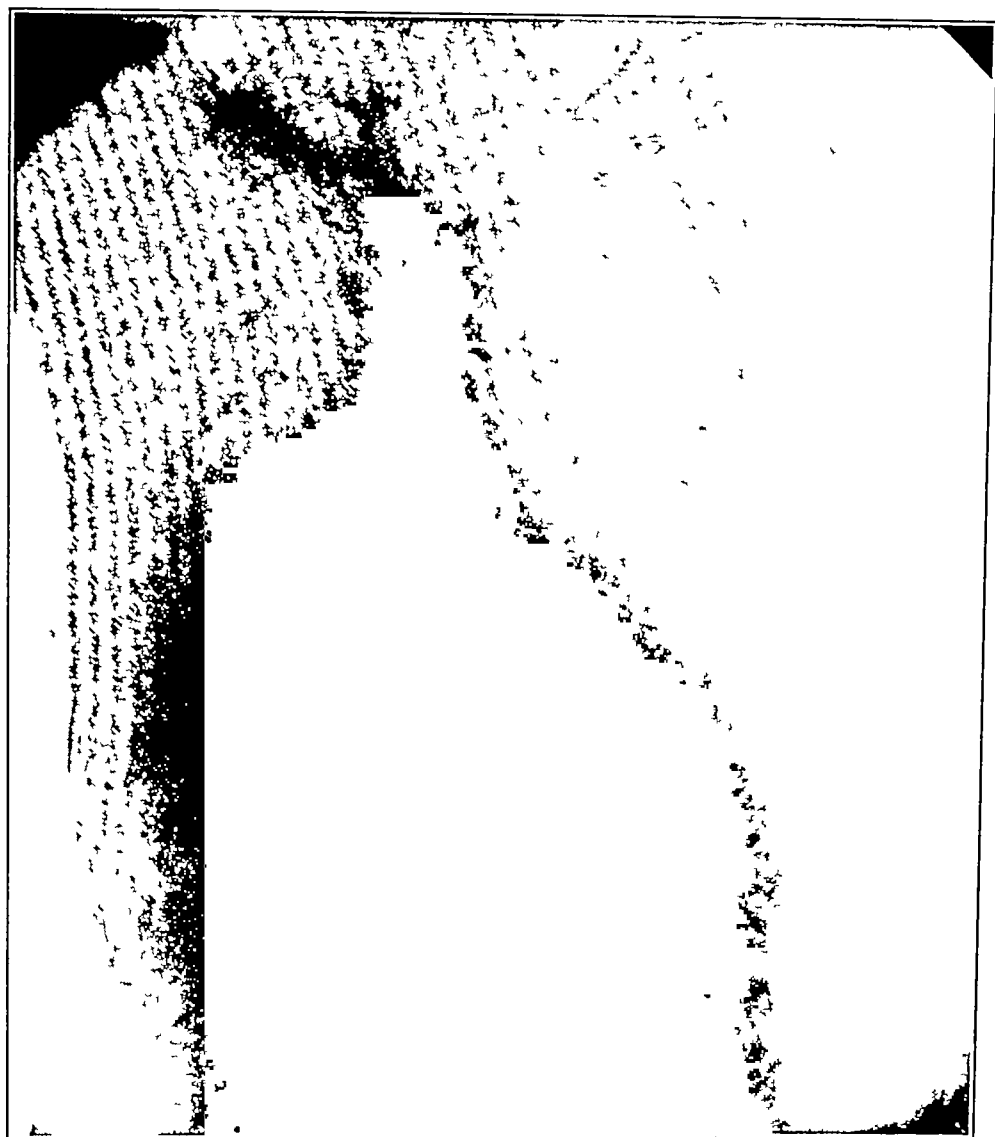


FIG. 4



On Feb 10th through paracentesis 1200 cc of fluid was removed, the specific gravity was 1024 *The Bence Jones reaction was positive* (Dr Killian)

On Feb 14th the blood report was Hem 94%, E 4,500,000, L 5000, P 71, L and 1 25, Mo 2, Bas 1, E 1 The blood chemistry Urea N 17.1, uric acid 15, sugar 68 mgr

On Feb 21st, 1928, the X-ray report says more pleural involvement in the right chest with further destruction of the ribs previously noted The fourth and sixth ribs on the left side showed an increased destruction (Fig 5)

On Feb 26th, patient complained of pains in the lower ribs on both sides The examination proved both fifth ribs very sensitive to touch The cachexia is progressing rapidly Still the blood report does not show any anemia Haem 85, E 5,500,000, L 7100, P 74%, L and 1 19%, Mo 3%, E 4%

While the patient used to move around her room, and sometimes sit for few hours in a chair, she now keeps quietly in bed, avoiding any other position than the one of lying flat on her back

On March 2nd, I made a more thorough inquiry about her condition and a renewed complete examination The complaints were a shortness of breath which is less intensive when the pains are localized in the upper back (shoulder and shoulder blades) than when they involve the lower right ribs A certain catching of the breath, corresponding to the lower left ribs, is always present, whereas at the beginning of the disease, was only of short duration No appetite, nausea quite frequently Constipation, but no pains in the abdomen, unless after a laxative There is no burning passing the water but she has to void often No cough sleep very poor, unless with the help of hypnotics Patient complains also of a tired feeling in the arms, more so than in the legs The motion in the arms gives pains in the chest The speech is quite difficult, partly through shortness of breath Walking is very difficult, with increased dyspnea and choking feeling While sitting in a chair the patient has pains in

both lower parts of the chest, left more than the right, the right trochanter is also painful (the mentioned spots and sometimes the right and left big toe would become very painful for a short period of time, showing redness on the surface and a certain amount of swelling, like in gouty attacks and then disappear, with no X-ray findings) There is a numbness in both arms Examination shows temp 98.8°, blood pressure 110/80, pulse 104 Patient is sitting in a chair, appearance cachectic, dyspnea, frequency 36 The inspection of the chest shows great emaciation, the scaleni and pectoralis muscles pulled strenuously with every breath, the intercostal spaces show inspiratory depressions The whole chest very sensitive to touch, especially the lower ribs, the lower part of the sternum, the processes spinosi of the 1st, 2nd, and 3rd dorsal vertebrae The percussion gives dullness from the upper margin of the third right rib and from the middle of the scapula down Compression breathing to be heard over the third and fourth intercostal spaces, no breathing sound or vocal fremitus over the dull part of the right chest The left lung base adherent from a previous basal pleurisy, the breathing sounds over the left lung negative The heart action is very fast, no murmurs, no arrhythmia The abdomen meteoric, due more to the opiates the patient gets in order to obtain some sleep, than to any other source The parasthesia of both arms, left more than the right, is very pronounced

On March 6th the fluid in the right chest has reached anteriorly the lower margin of the right second rib and the spinous scapula posteriorly Through renewed tapping of the pleural cavity 800 cc of fluid was obtained Blood was taken the same day for the detection of Bence Jones protein in the serum Report on Bence Jones protein (Dr Killian) was positive in the chest fluid faintly positive for the blood serum

X-ray examination on March 7th reports pleural effusion still present in the right chest Advanced destruction areas in the left ribs, sixth rib on the right shows increased destruction (Fig 6)

Blood examination report Hem 100%



FIG 5

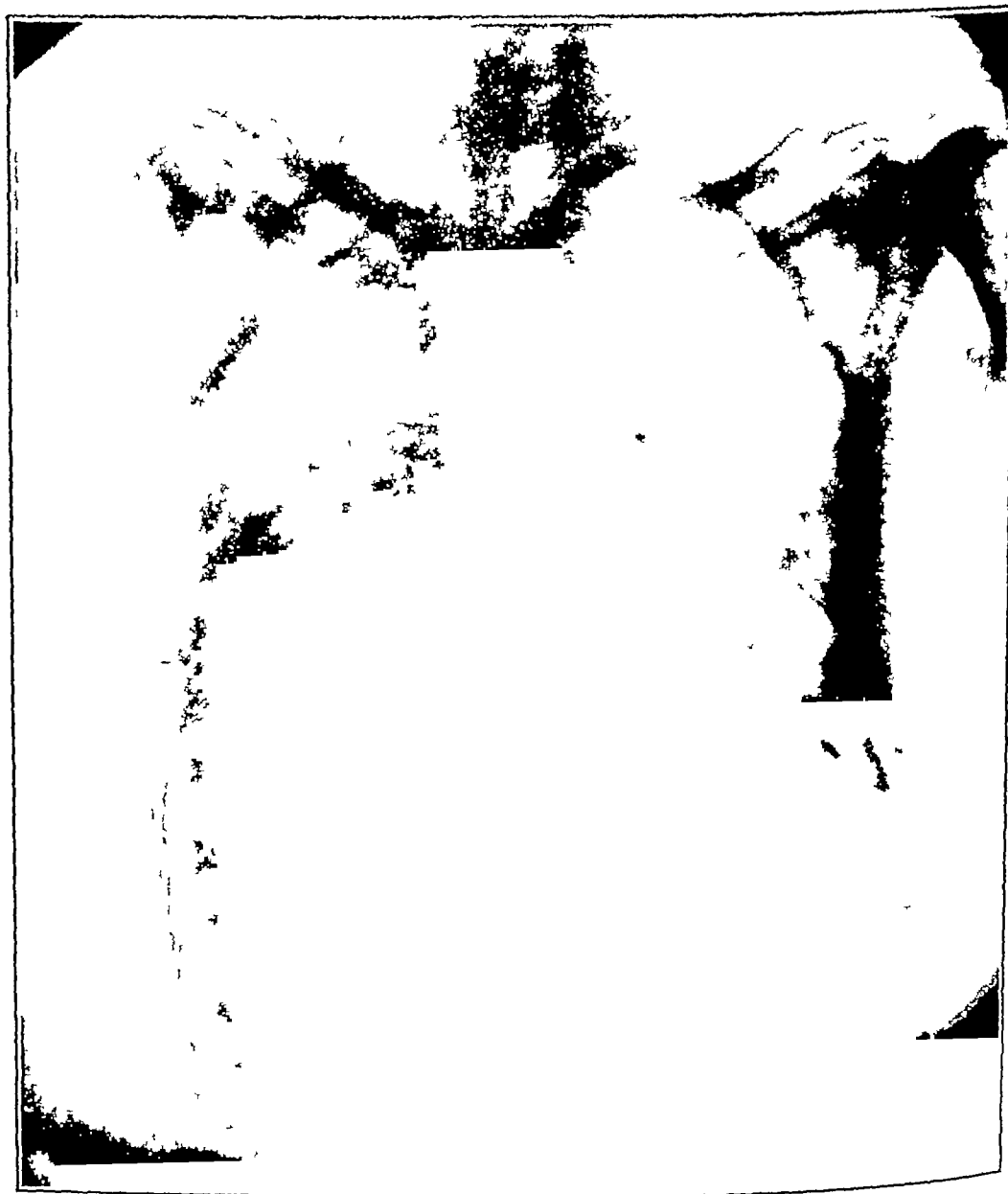


FIG 6

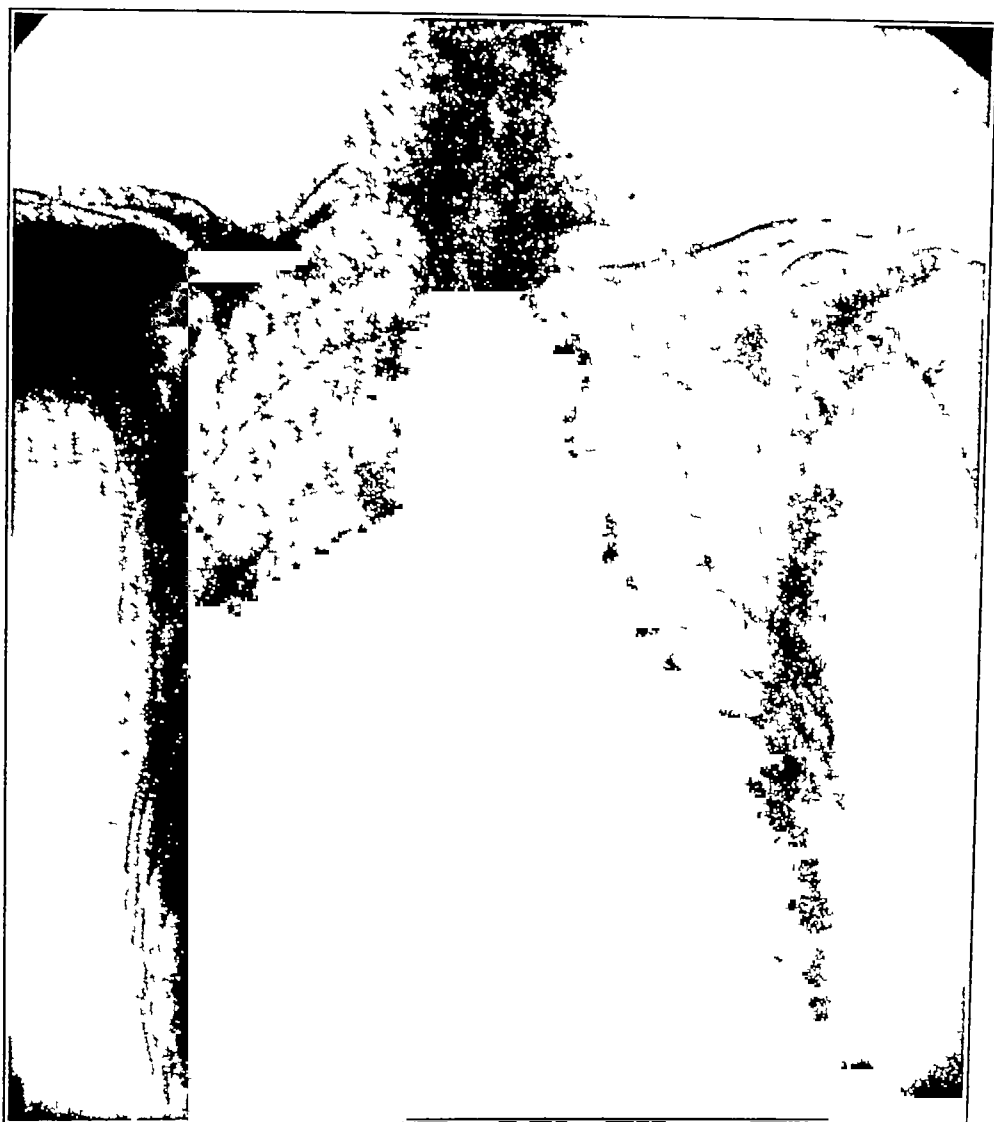


FIG 7

E 5,000,000, Leukocytes 7800, P 63, L and 1 32, Mo 4, E 1 On March 23rd Hem 85%, E 5,000,000, L 12,000, P 78, L and 1 17, Mo 2, E 2, Ba 1

March 25th the dyspnea is increasing, excessive pains in the lower left ribs, pt very restless, morphine needed every night to induce some sleep

On March 26th another paracentesis was performed, 800 cc of fluid was obtained. The dullness decreased to the upper margin of the sixth right rib anteriorly, and to the angulus scapulae posteriorly. Breathing was easier. Temperature normal, Pulse 120. Blood was also taken and the bloodserum showed a positive reaction for Bence Jones protein, as did the pleural fluid. The urine of the same day, for the first time since the beginning of the observation, was positive for Bence Jones protein, 291%. The X-ray report, from pictures taken after the removal of the fluid on March 26th, reads: Pleural effusion remaining in the right chest. There is a mass around the right root about the size of an egg, which has been present throughout the series but shows more definitely in the recent films, the fourth rib left shows more destruction and the sixth rib on the left side is practically destroyed. There are numerous changes throughout the chest (Fig 7)

*Diagnosis (Dr Pound)* Multiple Myeloma with progressive rib destruction, pleural and lung involvement

The blood count on April 6th Hem 96%, 5,000,000, leukocytes 9100, P 72%, L and 1 27%, Mo 1%

The temperatures to April 12th were normal. The cachexia rapidly progressing, the pulse getting faster and irregular, the patient refuses any nourishment. The pains were so excessive that we had to keep her the last days under morphine. After a comatose stage of one day, the patient died on April 13th, 1928.

The post mortem was not possible, not having the consent of the family.

The therapeutic measures during the time of her illness were roborantia, quartz light, camphor in oil and mirion, with no advantage. The deep X-ray therapy as one would suggest has not met with the

approval of the specialist in the case, the conditions being too advanced. Intravenous Thorium X injections, which I would have liked to try, were not available. There is certainly for myeloma a more definite possibility to reach any therapeutic success than in any other malignant tumor.

The differential diagnosis from secondary multiple myeloma was the absence of the primary tumor, from tuberculosis of the ribs with pleurisy, the absence of any tuberculous symptoms, from rachitis, osteomalacia, osteitis deformans, caries of the vertebrae, isolated vertebral tumors, the X-ray findings and the absence of the Bence Jones protein in the urine. Senile osteoporosis leads also to spontaneous fractures, the pains are not very intense. Chloroma has a leukemic blood picture, and the localization is mostly in the flat bones of the skull.

The most characteristic symptoms for myeloma are Bence Jones protein in the urine, the cachexia, the spontaneous rib fractures and deformities and the intensive periodical pains, the X-ray findings, the recurrent fever, the absence of any too pronounced changes in the blood with the exception of the slight myelocytosis and the presence of basophiles (common occurrence in all malignant tumors).

## CONCLUSIONS

The reported case of primary multiple myeloma presents certain peculiarities, which may be of interest.

The ribs alone were found affected, in none of the other bones were tumor formations detected. The destruction of the ribs led to the pleural effusion, not a common occurrence.

The pleural fluid contained Bence Jones protein.

The blood serum and the urine contained also Bence Jones protein, the urine only toward the end of the patient's life.

The X-ray examinations have helped to the early diagnosis, when

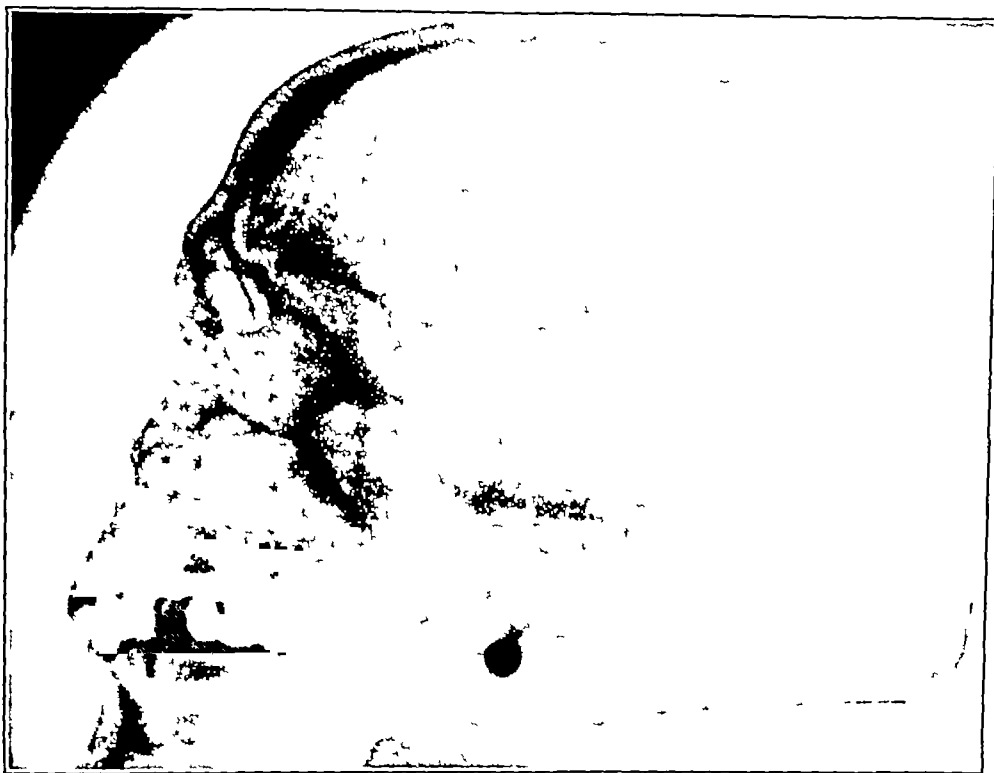


FIG 8

the other symptoms were not evident as yet

The hematological findings in this case were Normal hemoglobin and red cell count, a normal leucocyte count in the fever free period, a slight leukocytosis with the accumulation of the pleural fluid. An increase in the percentage of the eosinophiles (to 5%), of the basophiles (to 4%), the appearance of neutrophile myelocytes (up to 6%), a polynuclear leukocytosis with the pleural complication.

The recurrent type of fever since the appearance of the lung complication.

The temporary pericostal inflammation over both trochanter and the big toes.

Paresthesia of the upper extremities.

The progressive cachexia.

The duration of the disease since the first symptoms, has been a little over one year. The early diagnosis by means of X-ray should be attempted in every suspicious case (some are taken for intercostal neuralgias) and deep X-ray therapy, radium or mesothorium irradiations tried from the beginning. Intravenous injections of Thorium X are supposed to be of value.

The therapeutic measures in this case were of no value. I have used quartz light, arsenic and iron, mirion, sedatives and narcotics toward the end were unavoidable.

The multiple myeloma damages the bone marrow the most important blood producing organ. While in some instances the multiple myelomas



Fig 9



FIG 10



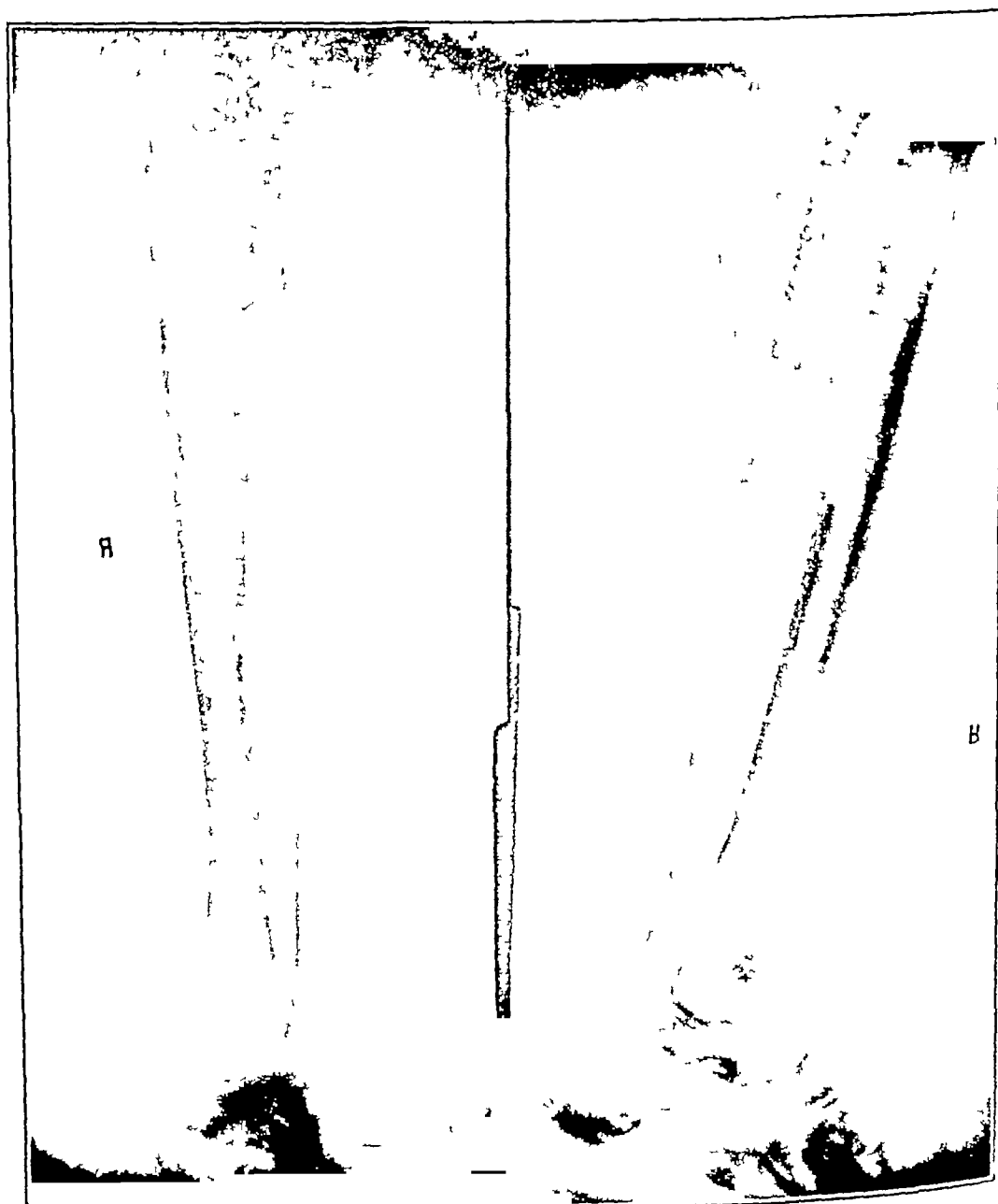


FIG. 11

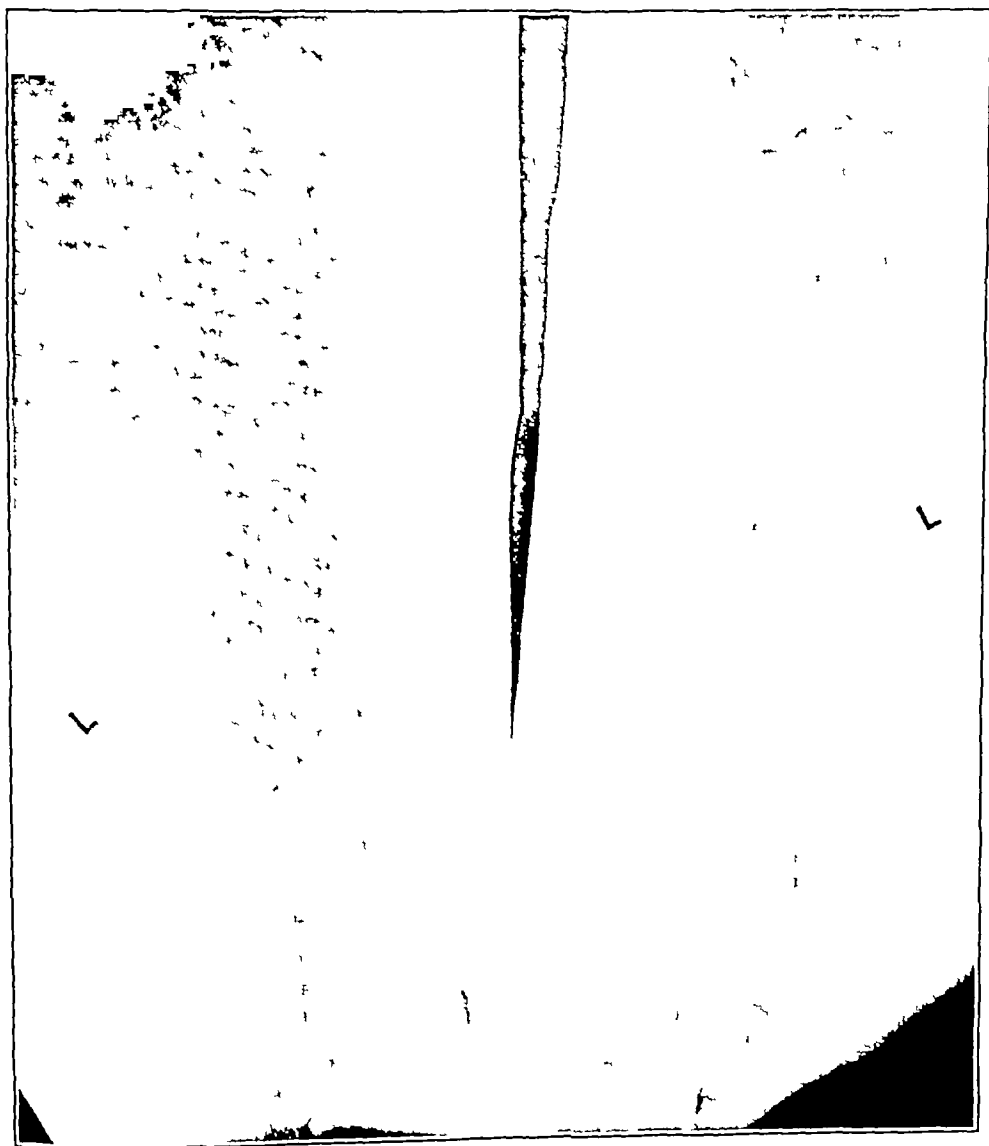


FIG 12

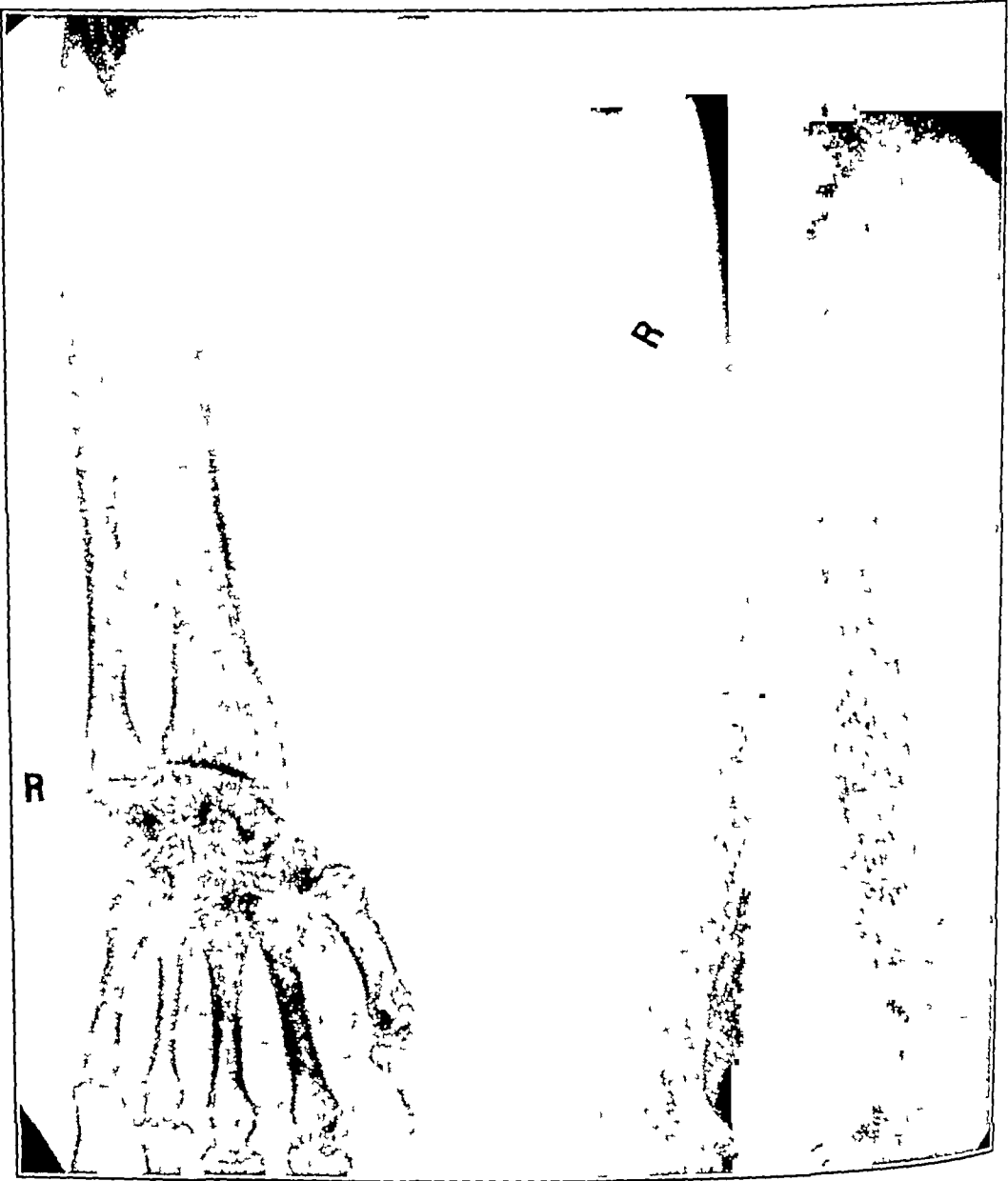


FIG 13

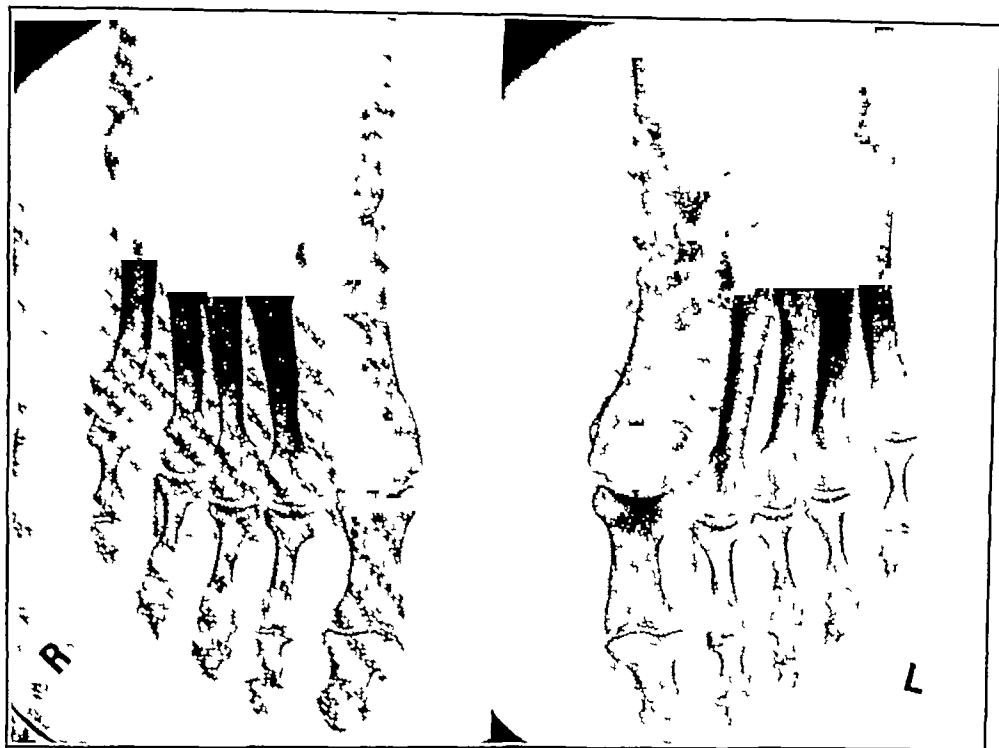


FIG 14

differ in their clinical manifestations from the secondary multiple tumor formations in the bone marrow, in others their clinical picture is identical

The myelomas, depending upon their localization and distribution in the skeletal system, upon the intensity and direction of their growth, their anatomic relation to the compact bone substance present a diversity of symptoms

In some cases the symptom complex is very characteristic (Kahler) very severe pains, neuralgic like, over the thorax mostly in the ribs appearing in periodic intervals of several days. Sometimes, a deviation of the spine or a definite kyphosis, the patient appearing smaller, will make the differentiation from osteomalacia

difficult. The ribs fracture at the least physical effort

Secondary to such fractures a pleural effusion may follow (an exudate through inflammation of the pleura) accompanied by fever

The elimination of the Bence Jones protein, which appears in the urine of 80% of the myeloma cases, although sometimes toward the end of the patient's life usually one of the first symptoms, is regarded as the cardinal symptom of the disease. There is a very pronounced cachexia. The blood findings as described in the literature show little pathology except anemia

Kahler in 1889 first described the above symptoms of the disease and held the circumscribed homologous tumor formations of the bone marrow responsible for the clinical symptoms

of the disease. The histological examination of his case (Chiari), showed that the tumors were multiple endotheliomas of the bone marrow. Further research has shown that primary multiple myelomas of various histological structure present the same clinical picture.

The case of Kahler was of a physician, 46 years old, whose disease started in 1879 with pains in the right side of the chest, which increased during respiration. The pains disappeared gradually, (few days), and returned after months localized in one point of the right 3rd rib, disappearing again after four weeks,—till 1880, in April, when the pains appeared in different regions, (ribs, vertebrae, left shoulder, left upper arm), increasing during motion. The processes spinosi of the vertebral column were sensitive. In March, 1881, a swelling appeared in the left fifth rib, which subsided after several weeks. Such periodic swellings, in different ribs, occurred often in the next years. Several nerve plexi became sensitive. In the urine the Bence Jones protein was positive. In 1882, the fingers of the hands, the cristae ossis ilei and the back of the head, became very painful, the gradually increasing cachexia forcing the patient to stay in bed. Paresthesia of the lower extremities, cardialgia and vomiting, enteralgia and asthmatic attacks, paroxysms of cough and chills complicated the condition. In the sixth year of the disease, a kyphosis in the upper dorsal segment started, the thorax became short, the vertebral column bent over more and

more, the chin showed a decubitus from pressing on the chest.

The third right rib fractured spontaneously. Finally came disturbances of the sensorium, hallucinations and loss of consciousness. The cachexia became very pronounced, though still only a slight anemia.

Patient died after 8 years of illness. The post mortem showed numerous bone tumors which were called multiple myeloma. (Chiari held them for multiple bone endotheliomata.)

### ETIOLOGY

Trauma has been advocated as etiology by Gluzinski and Reichenstein, Heldt, Simmonds, Schennan, Weiss, Winkler, pains before the trauma, in some cases, a long interval between trauma and symptoms (Hopkins and Savory, Marchand, Funkenstein), trauma and symptoms at the same time, in the case of Ewald's rib fractures in Versé's case, where trauma happened 5 months previously. No trauma mentioned in Wallgren's cases. Infections accepted as etiology by Bechtold, Klebs.

Infections with fever in the cases of Hammer, Charles and Sanguinetti, Ellinger, Seegelken, Vignard and Galavardin, v Rusticky, Wieland and Zahn. The type of fever intermittent, due to the bone marrow process (Winkler), to bacteria in the blood (Beck and McCleary), or in diseased parts of the bone marrow (Bender, Madsen). Lues in the case of Bertoye. Lues and myeloma (von der Heide, Madsen, Wright, Parkes Weber).

Tuberculosis of the lungs (Abrikosoff, Zahn, Madsen, MacCallum,

Scherman, Saltykow, Taylor and Miller)

Primary anemia was thought to be the cause of the bone marrow changes by Grawitz

In the case reported the history mentions a form of anemia in the mother and trauma at the beginning of the disease (the rib fracture which followed the trauma, the bone marrow condition may already have existed)

The age between 50 and 55 is most frequent for myeloma cases, as seen in Wallgren's table, reporting on 98 cases of anatomically certain myeloma, the youngest case at 22 (Haberfeld and Lordy), the oldest described by Grosch in a 80 years old woman. The disease is more frequent in men

#### PATHOLOGY

According to the histological structure we distinguish two groups of primary multiple tumors of the bone marrow

(a) the true multiple myeloma, circumscribed, the cells of which appear normally in the bone marrow tissue (parenchyma cells, colorless blood cells or normoblasts)

(b) the second group of primary multiple bone marrow tumors which have their origin in the stroma of the bone marrow (connective tissue or blood vessels) sarcoma, endothelioma, enchondroma

The skeletal system in primary multiple myeloma presents deformities and spontaneous fractures. The thin corticalis at different places may resemble parchment. The tumors are mostly round, circumscribed, well demarcated from the surrounding bone marrow, gray, red or yellowish in color, resem-

bling in sections, the structure of lymphatic glands. The most frequent localisations are the ribs, the vertebrae, and the flat bones, which contain red marrow. The tumors grow often in the compact portion of the bones, replace it and push the periosteum out forming round deformities. In other instances the tumors do not grow in the compact bone substance and do not produce deformities, they can only be detected within the bone marrow by sawing the bones. In the former instance, the bones are very soft and easily breakable (the ribs especially), the tumor mass having the consistency of white brain matter or spleen pulp. Often in post mortem, on a superficial observation of the skeletal system, serious changes are found although one cannot macroscopically distinguish between the true multiple myeloma and the histologically differently constructed primary multiple bone tumors

The presence of multiple myeloma is detected through bone enlargements, especially of the ribs, also the skull, sternum and hip bones. In the vertebrae and large bones the tumors are not protruding, in the case of involvement of the vertebral column, only if the protrusion effects a compression of the spinal cord does it become clinically interesting

The sternum may become quite thick through the presence of tumor mass. Kyphosis and kyphoscoliosis of the vertebral column are also a frequent occurrence.

The term "multiple myeloma" was given by v. Rustitzky in 1873. He studied histologically and described one case from von Recklinghausen's

Institute The tumors in his case had the consistency of white brain matter and presented the appearance of hypertrophied lymphatic glands. Microscopically the tumors were formed of round cells with an opalescent protoplasm and one or two round nuclei, little different from the surrounding bone marrow cells. On account of the identity of the tumor cells with the bone marrow cell elements, Rustitzky named the tumors myeloma, and wanted to emphasize that they have nothing in common with the myelogenous bone sarcoma (Virchow), which show a great many giant cells. The fact that the multiple bone sarcoma grows in the surrounding tissue, while the myeloma is strictly limited to the bone system, is another differentially diagnostic important feature.

Zahn in 1885, finds the analogy between myeloma and leukemic or pseudoleukemic hyperplasia, naming the former myelogenous form of pseudoleukemia.

Sternberg while he admits analogous changes of the bone marrow through myeloma, as the ones in the lymphatic glands and the spleen through pseudoleukemia, places myelomas on account of their localization and appearance in circumscribed, tumor-like formations, among the tumors, and due to their anatomohistological peculiarities, distinguishes them from pseudoleukemia.

Naegeli agrees to the similarity of myeloma with aleukemic systemic affections.

Grawitz describes them under the chapter of aleukemic medullary hyperplasia.

Lubarsh sees in myeloma a systemic disease, very close to the leukemic and pseudoleukemic affections.

Schridde in his chapter on "The Blood-forming organs," describes myeloma as true bone marrow tumors, tumor-like hyperplasias of myeloid tissue, not easy to distinguish from leukemic myeloses (Myelosarcoma are those tumors, which while made of myeloid tissue, produce metastases in other organs).

Kaufmann calls multiple true myelomas primary tumors of the bone marrow, composed of bone marrow cells.

Ribbert says "In its structure the myeloma is close to lymphocytoma."

Pappenheim calls multiple myeloma a medullary form of pseudoleukemia, a systemic disease of the hemopoietic apparatus, of aleukemic nature.

Histologically, according to the kind of cells composing the myeloma, there are six different types of myeloma — 1) Myeloma composed of lymphocytes 2) of myelocytes, 3) of myeloblasts, 4) of plasma cells, 5) of erythroblasts, 6) a mixed myeloma, in which all bone marrow cells are represented.

There is a definite differentiation between the medullary pseudoleukemia, which does not affect the compact portion of the bones, and the true multiple primary myelomas, which destroy it through a progressive resorption. The cases in which this peculiarity is not mentioned may have died before the growth of the myelomatous tumors was strong enough.

From the pathological histological point of view we define primary

multiple myeloma as tumors localized in the bone marrow, mostly circumscribed leukocytomas, having a tendency toward malignant growth but seldom leading to infiltration of the surrounding tissue or producing metastasis. Under certain circumstances they may not appear as isolated systemic diseases of the bone marrow, but rather, of the whole hemopoietic apparatus.

This purely histological definition should not lead to conclusions of any etiologic relation between multiple myeloma and the leukemic or aleukemic conditions.

#### CLINICAL SYMPTOMS

The symptomatology of the primary multiple tumor formations in the bone system is practically the same, independent of the histological structure. The beginning of the disease is hardly noticeable. The patient very seldom knows the exact time when the first symptoms appeared.

In *Zahn's* case, intense pains in the region of the lower ribs and lumbar region followed exposure and strenuous work.

In *Hammer's* case, headaches were the first symptom, possibly due to the primary localization of the tumors in the bones of the head. In other cases the pains started in the bones of the extremities or in the spinal column. Such conditions are apt to be regarded as rheumatism.

Often a trauma is given as history, and the disease followed, supposedly, several weeks afterwards, (cases of *Winkler*, *Ewald*, *Abderhalden* and

*Rostoski* (after lifting a heavy load), *Gluzinski* and *Reichenstem*, *Hoffmann*, *Vance*). The trauma cannot be accepted as etiology, but helps to disclose the existence of the disease and the course may be hastened. The periodicity with which the pains appear and the pain-free intervals are characteristic. The localization is for the most part, in the thorax, vertebrae, hip bones, long bones, and only seldom in the head.

Cachexia very soon becomes pronounced but there are no signs of anemia.

The most evident symptoms are the bone deformities, such as deviation and bending of the spine, thickening of the ribs with nerve compression and spontaneous rib fractures. Thoracic deformities which impair the circulatory and respiratory functions produce dyspnea and cardiac oppression and may lead to secondary inflammatory conditions of the lungs, and so, to exitus, also, tumors in the vertebral column, with compression of the spinal cord tending thus to exitus. The patients reach the state when they cannot leave their beds, develop decubitus and die from some complication.

The duration of the disease is on the average, from six months to one and one-half years, although there are exceptions, as in *Marchand's* case, which lasted six weeks, or in *Sussmann's*, which lasted three weeks or in *Kahler's*, when the patient lived eight years. Men are more frequently affected than women, and generally between the ages of forty and sixty years.



## BONE SYMPTOMS

The tumors may not be detected *intra vitam* if they are very small or very few in number and do not produce any symptoms. Only in post mortems are multiple myelomas found in cases where they were not suspected.

The pains start in one bone and are most intense if the process involves the thorax, especially the ribs, giving a feeling of great oppression. The pains appear periodically or intermittently, increased through exertion. A severe sensitiveness of the bones is noticeable during pain paroxysms and also later. The intensity of the pains can be so great that the patient must keep to one position.

The patient of *Abrikosoff* started, as in my case, with pains in the left lower ribs, especially during motion. The percussion in such cases is painful.

The prominent symptoms (*Sternberg*) are,—very painful thickening of some of the bones,—sternum, ribs, skull, hip bones. The bone changes are seldom so evident as to be seen from a distance, except as in *Rusticki's* case, in which a tumor the size of a bean appeared on the left temporal side. It grew to the size of an apple, displaced the eye, injured the sight, perforated the bone and adhered to the dura mater.

Angular bending of the ribs occurs when the corticalis gets thin through the growth of the myeloma. Also, bending of the vertebral column, reducing the height of the patient, as in *Kahler's* case, who shrank to midget size. *Sternberg's* case had thorax deformity, the sternum S-

shaped, and the vertebral column in a half circle.

The nerve plexi can be damaged through pressure, with resulting paraesthesia and nerve paralysis. In myeloma of the skull a stuporous condition is a usual symptom. Compression myelitis (*Rusticki's* case) is followed by paraplegia, *incontinentia alvi et urinae*.

Spontaneous fractures of the ribs caused by moving in bed or by percussion or palpation, are a frequent occurrence, and they represent the early symptoms of the disease.

*Kahler's* patient suffered immensely from the slightest motion and even from breathing.

## SYMPTOMS OF THE NERVOUS SYSTEM

The nervous disturbances accompanying multiple myeloma may be the result of direct pressure of the tumors on a nerve plexus, the central nervous system, or in other cases of a toxic nature.

Paraesthesia is always a common complaint. Severe pains are localized in the bones seldom corresponding to one nerve. Skin hyperalgesia is a common symptom. Most important are the disturbances caused through compression of the spinal cord, followed by paraplegia, *incontinentia alvi et urinae*. Anomalies of reflexes are mentioned, without a definite pathology.

*Stokvis* mentioned in his case, paraplegia, speech and swallowing disturbances, salivation, trigeminus and facialis paralysis.

*Wieland's* case had hearing disturbances (labyrinth diseases).

*Rustitzky's* case started with a tu

mor in the right temple, which gradually displaced the eye

Quackenboss and Verhoff describe the protusion of the eye bulb through tumor pressure

### HEART AND LUNGS

The deformity of the thorax will bring about pressure symptoms of the heart and lungs

Terninal pneumonias are quite frequent and also hydrothorax

The digestive organs present also anomalies as anacidity, lack of appetite and intestinal paralysis (through direct cord lesions)

Cachexia is one of the most important symptoms, sometimes pronounced before definite bone symptoms are detected. A very severe general weakness, which begins early and progresses rapidly is another specific occurrence. The extremities are mostly affected, which forces the patients to leave the bed as little as possible

The temperature is mostly normal, although there are instances, where a recurrent fever appears, sometimes chills and sweats, (Hirshfeld)

### BLOOD FINDINGS

The bone marrow in myeloma is replaced to a great extent by tumor masses, some parts, through pressure, being transformed into red marrow, we would expect serious changes in the composition of the blood

A slight anemia is mentioned in most of the cases (Anemia reported by Austin, Beck and McCleary, Conti, Ellinger, Gluzinski, Haberfeld, von der Heyden Jacobson, Kahn, Kim-

merle King, McCallum, Madsen, Mieremet, Schutz, Sexsmith & Klein, Stumm, Weber, Weinberg and Schwartz, Wallgren (5 cases among 14)

Normal findings reported by Bombard, Christian, Thomas, Jellineck, Kahn, McConnell, Martini, Scarlini, Vance, Wright, Wallgren (5 cases)

The hemoglobin is found reported as low as 30% by Hertz and Jochmann-Schumm, 23% by Parkes Weber Normoblasts and megaloblasts are mentioned by Gluzinski and Reichenstein Lymphocytosis up to 60% and normoblasts in Voit-Salvendi and Hirschfeld cases

Myelocytes, as pathological cells, are cited by Saltikow Sternberg (21.8%), Parkes Weber, Wallgren Eosinophilia cited in 6 cases by Wallgren

Conti in his case mentions Hem 48%, Erythr 1900000, L 3400, (P 42%, E 4%, Ba 2%, L 14%, i 10%, Mo 22%, Myel 6%)

Arneth in his case found Hem 42%, E 2400000, L 10000. The percentage of the neutrophile polynuclears, was normal

Kahn reports a pronounced anemia in two cases 1) Hem 34% E 3200000, L 10200, (P 63% L and i 35%, Mo 2%)

2) Hem 30% E 2000000, L 4800, (P 49%, L 42%, Mo 9%), later Hem 18%, E 1584000, L 4200 (P 60%, L 36% Mo 3% Ba 1%)

Roman in his two cases observed in children finds Hem 28%, E 1900000 L 9400 (P 26 8% E 16% L 63 8% Mo 5 8% Mevl 2%) and Hem 40%, E 1500000,

L 9600 (P 22%, L 65%, Mo 8%, Myel 5%)

Sexsmith, found Hem 85%, E 3140000, L 8000, (P 56%, L 22%, Frans 18%, E 4%)

Martini, found Hem 70%, E 4877000, L 6000, P 61%, E 1%, Mo 10%, L and I 28%)

Kimmerle in his case Hem 70%, E 3760000, L 5700 (P 60%, L 30%, Mo 6%, E 1%, Trans 3%)

McCallum reports as findings Hem 52%, E 3548000, L 4500

McConnell Hem 80%, E 4720000, L 7200 (P 58%, L 7%, L 30%, Trans 5%)

### THE URINE

There is not another disease of the hemapoietic apparatus, in which the urine reports are of such importance. In some cases there is albumin and cylindruria, in a large percentage the appearance of the Bence Jones protein is of chief value. Up to 1910 (cases collected by Hirschfeld) 36 cases mention the presence of Bence Jones protein in the urine, while in 42 cases it was not detectable (in some, they may have neglected to look for it, in others the diagnosis of myeloma has been made only after post mortem)

Decastello found the protein in 2 cases of lymphatic leukemia, Askanazy also in a case of leukemia. Campbell Horsfall reports the presence of the protein in a case of gunshot under the knee, Zuelzer in dogs poisoned with pyridin

The substance will be found in diseases involving the bone marrow, seldom in leukemias most frequently in multiple myeloma. The cases of

Fitz (myxedema and albumosuria) and of Coriat (Bence Jones protein in the pleural exudate of a case of Korsakoff's psychosis and myeloma), are doubtful in the opinion of Hirschfeld

Bence Jones was the first in 1848, in a case of myeloma of Dalrymple and MacIntyre, to detect a protein which appeared in the urine, when heated to a temperature of 50 to 60 C, and which became soluble at a higher temperature (the case was diagnosed as osteomalacia fragilis rubra)

Stokvis in 1869, mentions the presence of the protein in a case of osteomalacia, Rustitzky in 1873, Kähler in 1889, Kaschker in 1894, report it in cases of senile osteomalacia

Seegelen in 1896, in a case of chondro-sarcoma with albuminuria, Senator, Rosin, Süßmann, in 1897 in clinically evident cases of multiple myeloma

Magnus Levy, in 1900, studied thoroughly the substance and found it to be a protein, not an albumose. Since then, we speak of a Bence Jones proteinuria instead of albumosuria

The protein is found in 80% of the primary multiple myeloma, hardly ever in metastatic bone tumors (Naunyn, Marcovici). The absence of the protein in cases of primary multiple myeloma, is mentioned by Scheele and Herxheimer, Collins, Wallgren (7 cases), while the presence is cited by Bradshaw (one year before the appearance of the tumors (an amount of 13.9 gr per day), Oftedal Cathcart (15 to 20 gr per day), Groves (63 gr per day). Auerbach Sexsmith, Henderson (15 to 20 gr)

Askanazy, Donetti, McCallum, McConnell, Buchstab and Schaposchnikow, Horsfall, Jochmann, Kimmerle (3 to 5%), Kahn in 2 cases, Wallgren (42 of the 118 cases in the literature, up to 1920)

The eliminated quantity reaches in some cases 70 gr per day, the amount decreases or can disappear entirely toward the end of the patient's life. The substance may derive from the tumors or through their damaging influence on the remaining marrow. The detection of the protein in the tumors or in the blood serum has been negative in the literature as reported by Hirschfeld. Since then, the pressure in the blood is mentioned by Jacobson, d'Alloco, Martini, in the spleen extract by Reach, in chloroma by Weinberger, in tuberculous osteoarthritis by Vidal, in myxedema by Jacksch, Fitz, in leukemia and in metastatic carcinoma by Boggs and Guthrie, in carcinoma ventriculi by Oerum, in ascite by Ellinger, in pneumonia sputum by Bradshaw, in bone marrow leukemia previously by Askanazy, in the pleural fluid by Goriat.

Decastello found serious changes in the kidneys accompanying the albu-

minuria (it is doubtful whether the kidney lesions are the primary moment allowing the passage of the protein, or the continuous passage of the protein damages the kidneys)

Massini finds that the amount of the excreted protein is equal to the amount of food protein taken.

(The reaction for the Bence Jones protein is very simple: the urine is tested for its acidity, acetic acid is added; if found neutral, then heated between 40° and 60° degrees C.)

A precipitate forms, which becomes soluble on further heating and reappears when getting cold. The substance gives all the color reactions for proteins.)

Up to 1914, 61 cases were reported by Kahn of true primary multiple myeloma, 70 cases with post mortem reports are accounted for by Kimmerle, Schumm and Fraenkel.

Martini's 206 cases may include some doubtful cases, since the very valuable contribution to the myeloma literature of Wallgren from 1920 reports only on 118 well studied cases followed by post mortem examinations.

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# Endocarditis Following Septic Abortion With Special Reference to Sub-Acute Bacterial Endocarditis\*

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**T**HAT endocarditis, particularly sub-acute bacterial endocarditis, may be a sequel of infections during or following pregnancy, has received comparatively little attention, although many have considered the hazards incident to a pregnancy complicating a previously existing endocarditis. Acute malignant bacterial endocarditis, occurring more or less incidentally as a part of puerperal sepsis, has been recognized, and instances of this sort are common in any large series of cases of puerperal infection. By presenting three new cases from the Department of Pathology of the University of Michigan, this paper will endeavor to show that not only is acute malignant endocarditis a dreaded complication of puerperal infection, but that months afterward a typical sub-acute bacterial endocarditis may furnish a fatal sequel to an infected abortion which has passed the stage of acute manifestation.

In considering acute malignant endocarditis the differentiations made by Libman (1) will be accepted. He divides bacterial endocarditis into

acute, sub-acute and chronic, considering the average course of sub-acute bacterial endocarditis as four to eighteen months, the acute cases being more fulminating. The infecting organism in acute endocarditis is usually streptococcus hemolyticus, although more rarely other organisms, such as staphylococcus, influenza bacillus, pneumococcus, etc., may be causative. The clinical course is that of a profound septicemia, with embolic phenomena as a prominent feature. Petechiae, sharp attacks of upper left quadrant pain, hematuria, etc., are seen. The physical findings on examinations vary somewhat according to the damaged valve. As pointed out by Libman (2), Herrick (3) and others, the process is particularly apt to attack a previously damaged valve. The following case is illustrative of this group.

*Case I* Mrs. E. I., age 25, entered the University Hospital on the Gynecology Service, December 23, 1924, complaining of fever and bleeding from the vagina. Four weeks previous to her admission she stated that she had inserted a catheter into the uterus in an effort to produce abortion. Following this she passed two large blood clots, but experienced no profuse bleeding. After this she felt well and was able to perform her housework for a period of two weeks. At

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this time she again passed blood clots and bled profusely from the vagina for four days. Then she had a chill with fever of about 104 degrees and nausea but no vomiting. In spite of the severity of her symptoms she did not go to bed, but continued with her household duties. Bleeding continued until her admission to the hospital.

At the age of 10 she had an illness which she characterized as "rheumatism," but she stated that her joints were never swollen or red. She had no pharyngitis, tonsillitis or quincy. Her catamenial history was negative and her last menstrual period was two months previous to her admission to the hospital. She had been married five years. Her husband was living and well. One child was living and well. There had been two previous abortions, one following a fall and the other induced by a catheter.

Physical examination showed the heart to be of normal size. Heart sounds were regular and of good quality. The first heart sound was replaced by a rough, low pitched, systolic murmur, heard best at the apex. The murmur seemed to extend back into presystole.

The abdomen was slightly tense in the lower quadrants. There were no masses, areas of tenderness nor muscle spasm. The spleen was questionably palpable.

Vaginal examination showed a foul, brownish discharge. The cervix was large and soft, showing a bilateral laceration. The uterus and adnexa were not palpated.

No petechiae were noted. There was no clubbing of the nails. No edema was present.

At this time the urine showed albumin four plus, many granular and hyaline casts, and strong tests for acetone and diacetic acid. The blood showed a secondary anemia, and a white blood count of 13,900 with 68% polymorphonuclear leukocytes. Blood culture was positive for streptococcus hemolyticus.

The patient was transferred to the Medical Service. During her stay in the hospital she had a septic fever, with chills followed by rise in temperature to between 103° and 105° with correspondingly rapid pulse and respirations. Repeated blood cul-

tures were positive for streptococcus hemolyticus. Four days following admission she developed a right panophthalmitis and a bilateral acute arthritis of the wrists. She gradually became weaker, sank into a stupor and died on December 29, six days after admission.

#### CONDENSED AUTOPSY PROTOCOL

Autopsy 97-AC. Prosectors Drs Simpson and Breakey. On external examination the body was seen to be that of a somewhat poorly nourished, but not emaciated woman of average build. Over the face were scattered pustules. The right eye showed purulent exudate covering the conjunctiva, with a clouding of the cornea so that the pupil could not be seen. The left eye was negative. Over the sacrum there was an area of decubitus measuring 5 x 4½ cm, appearing relatively fresh and covered by a dry reddish-brown crust. Herpes labialis was noted. There were no petechiae.

Examination of the brain showed no meningitis, but there was edema and congestion of the leptomeninges. The brain substance showed increased bleeding points and involving the left thalamus and part of the lentiform and striate nuclei was an area of softening measuring 2 x 2 cm.

On making the main incision 75 to 100 cc of thick fibrinopurulent exudate was found free in the peritoneal cavity. The pleural cavities contained no free fluid, but the pericardial sac contained about 40 cc. of thick purulent material. The heart was about the size of the cadaver's right fist. There was purulent exudate with some fibrin over the external surface. In the myocardium there could be seen pale localized areas appearing grossly as anemic infarcts, varying from 0.5 to 1 cm in diameter. On opening the heart vegetations which had the appearance of being recent were seen on all the cusps of the aortic valve. Both flaps of the mitral showed vegetations, which appeared somewhat older, along their free edges and around the attachment of the chordae tendinae. The valve flaps were definitely thicker than normal, apparently due to an older healed inflammatory process.

The lungs were similar to each other and both showed an acute congestion. No infarcts were found.

On examination of the abdominal organs, the spleen was found to be about twice normal size. The capsule was smooth and had a reddish-blue color. Three anemic infarcts were present, one of which appeared to be infected. The splenic pulp was congested, and the Malpighian corpuscles were not readily seen. The gastrointestinal tract showed a fibrino-purulent exudate over the serosa. In the upper portion of the caecum there was a patch measuring 6 to 8 cm in length where there was a diphtheritic membrane replacing the mucosa in an irregular pattern. The lymphoid tissue was hyperplastic throughout. A fibrino-purulent peritonitis was also present over the liver, which showed in addition considerable fatty change. The left kidney showed recent anemic infarcts. The parenchyma showed cloudy swelling.

The external genitalia were negative except for a thin leukorrheal discharge. The uterus was enlarged and soft. The tip of the finger could be inserted into the external os. There was a slight bilateral laceration of the cervix and slight eversion. The endometrium was bluish-red in color and in the fundus midway between the orifices of the Fallopian tubes was a mass measuring  $3 \times 1 \times \frac{1}{2}$  cm, which had the appearance of retained, necrotic placenta. The uterine cavity was covered by a blood-stained fibrinous exudate. One tube was tightly adherent to the posterior surface of the uterus. One ovary showed a large corpus hemorrhagicum.

#### MICROSCOPIC EXAMINATION DR WARTHIN

*Heart* Active streptococcus endocarditis on an older thickened endocardium. Streptococcus abscesses in myocardium. Older areas of fibrosis in myocardium. Marked fatty degenerative infiltration, both subepicardial and subendocardial. Localized acute fibrino-purulent epicarditis over abscess in the myocardium. Abscess in subepicardial fat. Marked tiger heart.

*Uterus* Infected placental site. Necrotic

decidua. Diffuse diphtheritic endometritis. Streptococcus infection following abortion.

*Fallopian Tubes* One shows an acute perisalpingitis with plications infiltrated with polymorphonuclear leukocytes. Other tube practically normal.

*Vagina* Acute vaginitis.

*Pathological Diagnosis* Streptococcus septicopyaemia (following self induced infected abortion). Diphtheritic endometritis. Acute purulent salpingitis. Generalized fibrino-purulent peritonitis. Acute mitral and aortic thrombo-endocarditis. Multiple streptococcus emboli with recent infected infarcts in spleen, kidneys, myocardium and brain. Localized acute purulent meningitis and pericarditis. Right-sided purulent panophthalmitis. Acute diphtheritic colitis. Pyoderma of face. Herpes simplex labialis. Acute passive congestion and parenchymatous degeneration of all organs. Tiger heart. Old appendectomy scar. Decubitus.

Cases similar to this are numerous in the literature. Westphal (4) reported such a case in 1861, and in 1872 Virchow (5) reported a series of such cases, and pointed out the importance of endocarditis as a phase of puerperal sepsis. Recently, Mathias and Pietrusky (6) in analyzing 55 cases from the Pathological Institute at Breslau found 7 cases of fresh endocarditis. The illustrative case cited has all the clinical features of an acute endocarditis. The source of the infection is readily discernible as is usual in acute endocarditis. The rapid course, blood cultures positive for streptococcus hemolyticus and embolic phenomena, are all typical. The necropsy findings were characteristic.

throughout and established the connection between the infected abortion and the endocarditis

Sub-acute bacterial endocarditis shows a definite clinical difference from the acute type. The onset is characteristically insidious as compared to the more sudden onset of acute endocarditis. A general malaise, weakness, and lack of tone are usually the first symptoms. At this time there is usually an irregular fever, and often chills, but the patient is often able to perform her duties. What might be characterized as the terminal stage of the disease may be ushered in by embolic phenomena, and these are nearly always present at some time before death. Particularly are petechial hemorrhages usually seen at some period during the patient's illness. Blood cultures are frequently positive, although cases are reported with a typical clinical course and characteristic necropsy findings where the blood culture has been consistently negative. The course of the disease has generally been considered to be progressively fatal although Libman (7) has reported clinically cured cases. The duration varies from six weeks up to two or three years in exceptional cases. Often there are periods of recession of the disease followed by relapses, although the condition may be steadily progressive. The following two cases are submitted as typical sub-acute bacterial endocarditis following infected abortion.

*Case II* Mrs. M. C., age 19, entered the Internal Medicine Service of the University Hospital September 14, 1919, complaining of weakness and loss of weight. She was married and had one child 15 months old. As

a child she had measles and chicken-pox with good recovery. At the age of 12 she had typhoid fever, and stated that she was very ill for several weeks. Since that time she had enjoyed good health until the onset of the illness which caused her to come to the hospital. Her health since marriage had been as good as previously.

In February, 1919, she was pregnant about two months. Following the advice of a neighbor, she induced an abortion by passing a catheter, which she had made no attempt to sterilize, into the uterus. The abortion followed three days after the instrumentation. At this time she felt "sick at her stomach," and for a period of two weeks she had fever and several chills. She had never felt well since that time. There was a thick yellowish discharge from the vagina, but she experienced no pain except for painful urination for a short time. She had noticed loss of weight, although she did not know how much, and said her heart pounded and was irregular. These symptoms increased and she became weaker until finally she consulted a physician, about August 1, who put her on a liquid diet. She followed this treatment at home for three weeks and then entered a hospital in another city where she remained twenty days, steadily growing worse. At the end of that time she came to this hospital.

Physical examination showed a small woman of anemic appearance, with a faint flush over the cheeks and a slight cyanosis of the lips. The nodes of the posterior cervical chain were slightly enlarged and tender. There was a bounding pulsation of the great vessels of the neck with definite venous pulse.

Examination of the heart showed the apex beat to be visible in the precordium. The cardiac rhythm was regular but rapid. The first sound at the apex was ringing and accompanied by a soft systolic murmur. Immediately following the first sound and replacing the second sound was a loud blowing diastolic murmur lasting throughout diastole and well transmitted to the axilla. Over the aortic area there was a loud murmur lasting throughout systole and diminishing

ately followed by an equally loud murmur lasting throughout diastole

Examination of the lungs show impairment of percussion resonance at both bases. Breath sounds in these regions were faint and distant, and deep inspiration brought out a coarse friction sound. Examination of the abdomen was negative. Neither liver nor spleen could be felt. The fingers showed clubbing and curving of the nails. There was no edema of the extremities. No petechiae were seen.

During her stay in the hospital, she had a rise in temperature every afternoon. Six days after admission the patient complained of pain over the heart and experienced difficulty in breathing. The next day she was drowsy and during the afternoon she had the usual rise in temperature, became restless, and the pulse became more rapid. The next morning she was dyspneic, cyanotic, and showed a very slow labored pulse. Respirations gradually became slower and more labored, and she died quietly at 6 55 A M. September 22, eight days after entering the hospital.

#### CONDENSED AUTOPSY PROTOCOL

Autopsy 26-X. Prosector Dr. Weller. The body was that of a young adult female of slight build, showing fair nutrition, but marked pallor. The main incision showed no free fluid in either abdomen or chest.

The heart was markedly enlarged and showed no evidence of pericarditis. On opening the heart, the mitral cusps were seen to be beaded with organized and ulcerated vegetations. In the right cusp there was an aneurysm measuring 5 mm in diameter. All the cusps of the aortic valve showed an extreme degree of ulceration, one being eroded until only about 3 mm remained. From the edges of this extended stringy masses of fibrin. These vegetations extended up into the first portion of the aorta.

The lungs showed congestion but there was no consolidation. The abdominal examination showed a spleen four times normal size. The splenic pulp was hyperplastic, and there was marked congestion. There was one small anemic infarct measuring 3 x 5 mm. The kidneys were slightly

larger than normal. There was well marked cloudy swelling, and in the left kidney a small area of partly healed anemic infarction. Otherwise the abdominal examination revealed nothing of interest.

Coming from the vulva was an abundant purulent discharge, smears of which showed streptococci and bacilli. There was a small amount of exudate over the endometrium, but no severe process. The uterus was of about normal size. Ovaries were normal in size and showed no large corpora lutea.

#### MICROSCOPIC EXAMINATION DR. WARTHIN

*Heart* Fatty infiltration with serous atrophy. Marked atrophy and fatty degenerative infiltration of heart muscle. Organizing vegetations. Sub-acute endocarditis.

*Spleen* Marked chronic passive congestion. Lymphoid atrophy. Exhaustion of germ centers.

*Kidneys* Cloudy swelling. Atrophy. Congestion. Serous atrophy of the subpericardial fat. Areas of chronic inflammation. Fresh anemic infarcts.

*Uterus* Endometrium atrophic. Small leiomyofibroma.

*Ovaries* Chronic ovaritis and periovaritis. Imperfectly resolved corpora fibrosa with calcification.

*Tubes* Negative.

*Pathological Diagnosis* Sub-acute thrombo-endocarditis of mitral valve with valvular aneurysm. Ulcerative endocarditis of aortic valve. Aortic stenosis and insufficiency. Cardiac dilatation and hypertrophy. Anemic infarction of spleen and kidney. Severe secondary anemia. Serous atrophy of fat tissue. Marked fatty heart. Tiger heart. Passive congestion and parenchymatous degeneration of all organs. Streptococcus septicæmia (post-abortion).

*Case III* Mrs. E. O., American housewife, of 18 years, entered the Neurological Service of the University Hospital on the

st of November, 1927, complaining of paralysis of the left side of the body, pain in the right calf, and general malaise and weakness.

The patient was married at 13. She had one child 3 years old, living and well. She had had about seven self-induced abortions, the last one in July, 1927, when she was about 4 months pregnant. She was taken to a hospital at that time. Ever since that time she felt below par, although she had no definite symptoms with the exception of a foul discharge from the vagina. About three weeks before entrance, after pumping a pail of water and walking back to the kitchen, it was noticed that the right side of her face was pulled out of shape. The left arm and leg became paralyzed and she was unable to walk. She was not unconscious. She was again in the hospital a short time and partially regained the use of her left leg. The left arm and the right side of her face remained paralyzed.

Physical examination disclosed a well-nourished and well-developed young woman of poor mentality who cooperated fairly well. She did not, however, know her age exactly. Examination revealed a hemiplegia, most marked in the face and arm, the patient having partial use of the left leg sufficient to enable her to stand and walk unaided. The heart was slightly enlarged on percussion. There was a systolic murmur heard over the aortic area which was blowing in character and a very faint diastolic murmur. The pulse was of the irregular type, the blood pressure 135/20. The liver and spleen could not be palpated. Cause of voluntary abdominal rigidity. Physical examination revealed retroversion of the uterus, which was enlarged and boggy. There was a brownish discharge which was old.

Blood Wassermann was negative. On the blood and blood culture showed Gram positive cocci, probably streptococcus viridans. The urine showed a moderate amount of albumin, hyaline and granular casts, occasional red blood cells and many white blood cells. The blood showed hemoglobin, 50%, red blood cells, 2,500,000, white blood cells, 10,000, differential — polymorphonuclears

73%, lymphocytes, 13%, endotheliocytes, 8%. The electrocardiogram showed marked sinus tachycardia, but was otherwise normal. The X-ray on November 23rd showed cardiac enlargement, flattening of the left auricular curve, and clear lung fields.

The temperature fluctuated from 100° to 102°. During the latter part of her stay in the hospital her pulse averaged about 130, respirations, 40 to 68. On November 29th, the lungs, which had previously been clear, revealed râles and bronchial breathing in the lower right chest and a somewhat more marked involvement of the left. The liver at this time was palpated one hand's breadth below the costal margin. Her symptoms became progressively worse and she died December 1st.

#### CONDENSED AUTOPSY PROTOCOL

Autopsy 103-AF. Prosectors: Drs. Well-er and Fortune. The body was that of a well developed young adult female, showing no evidence of loss of weight. The skin had a noticeably gray tinge. There was lack of tone in the muscles of the left side of the body. Rigor mortis had not set in. Edema was present in both ankles, but more marked on the left.

In the right temporal lobe there was an area of softening measuring 5 x 5 x 5 cm, extending back into the basal ganglia, giving an area of softening in the floor of the right lateral ventricle. The right cerebral peduncle also showed an area of softening.

The heart was much larger than the cadaver's right fist, measuring 12 x 10 x 5 cm, and weighing 410 gms. There was a small soldier's spot on the anterior surface of the right ventricle and on the posterior aspect of the left ventricle there was a sharply localized area of adhesion between the parietal and visceral pericardium. On opening the heart there were many ulcerating vegetations seen extending along the edge of the aortic flap of the mitral valve for a distance of one centimeter. One centimeter above this line of vegetations there was a nipple-like projection 5 mm in its diameter extending into the left auricle. On investigation from below this was seen to be an aneurysm of the flap. In the below

the cusps of the aortic valve were numerous vegetations, completely surrounding the orifice and extending up onto the cusps. This process was much more marked than on the mitral valve. In the right ventricle on the septum, just opposite the mass of vegetations described below the aortic valve, there was a projecting mass of vegetations, which proved to be a mycotic aneurysm extending through the septum from the left heart. This aneurysm involved the flap of the tricuspid valve adjacent.

The lungs showed a brownish color, but not the firmness of induration. There was a marked congestion. Both lungs contained hemorrhagic infarcts, the largest of which was in the lower lobe of the right lung, and had a base 8 cm in diameter with a fibrin-

nous pleuritis over the surface. The pulmonary vessels contained thrombi, some of them old and yellowish-white in color. On section of the spleen numerous small subcapsular infarcts were seen. The kidneys showed both old healed infarcts and more recent infarcts, some of them very fresh.

The cervix uteri showed a large polypoid mass projecting through the external os. The upper attachment of this mass was in the uterine cavity at the right upper pole. This was covered by purulent exudate and had the appearance of an infected fleshy mole. The endometrium was hyperplastic and congested. The left ovary showed a large corpus luteum. The tubes appeared negative except for congestion.



FIG. 1 Heart from Case III, showing vegetations on the aortic valve

## MICROSCOPIC EXAMINATION DR. WARTHIN

*Bram and Meninges* Marked congestion and edema. Localized meningeal reaction over the areas of softening. Multiple large areas of anemic softening scattered throughout the brain in both cerebrum and cerebellum. Most of these are very recent as there is very little proliferation about the borders. No sclerosis of meningeal or cerebral arteries.

*Heart* Subepicardial fatty infiltration. Diffuse fatty degenerative infiltration, most marked under the endocardium. Extreme tiger heart. Muscle fibers are atrophic. Subacute bacterial endocarditis, still in active stage. Sclerosis of endocardium, with fresh vegetations on surface containing large bacterial colonies. At the base of these vegetations small tears extend through the thickened inflamed endocardium—first stage of aneurysm formation. Coronaries show slight lipoidosis of intima. No areas of either active or healed myocarditis.

*Lungs* Extreme congestion and edema. Multiple thrombosis of pulmonary veins. Multiple hemorrhagic infarctions. Extreme edema. Numerous pigmented "Herzfehler" cells but no induration of lungs. Areas of marked atelectasis with acute purulent bronchitis and beginning broncho-pneumonia. Fat stains show no fat emboli.

*Spleen* Extreme congestion. Multiple infected anemic infarcts. Infected emboli. Marked necrosis of the splenic follicles.

*Kidneys* Congestion. Atrophy. Slight cloudy swelling. Very few scarred glomeruli, except in areas of healed infarcts. Multiple anemic infarctions in all stages, some wholly recent, others healing. Fat stains show practically no lipoidosis.

*Cervix of Uterus* Severe glandular erosion. Chronic catarrh.

*Body of Uterus* Localized polypoid cystic glandular hyperplasia. Extreme congestion. Some blood pigment. Vessels show resolution—post pregnancy. Incomplete resolution. Cavity of uterus filled with a fleshy mole containing necrotic and still living chorionic villi decidua and infected blood clots. Infected retained placenta fol-

lowing abortion. In the uterine and vaginal plexus there are infected thrombi.

*Ovaries* Unresolved corpus luteum. A few cystic follicles.

*Tubes* Subacute inflammation.

*Pathological Diagnosis* Septicopyaemia (streptococcus). Retained infected abortion. Sub-acute septic vegetative endocarditis involving aortic and mitral flaps. Valvular aneurysm of mitral cusp. Mycotic aneurysm between root of aorta and right ventricle. Multiple embolic infarcts of brain, spleen, kidneys, lungs and abdominal wall. Early pyaemic abscess formation. Marked fatty degenerative infiltration of heart muscle. Extreme nutmeg liver. Marked passive congestion of all organs. Simple colloid goiter.

## DISCUSSION

In both of these cases it will be noted that from a clinical point of view the onset was insidious and not accompanied by characteristic symptoms. This period preceding the onset of serious symptoms was long in one case six months in the other case more than four months. In Case III brain embolism initiated the final stage of the disease in Case II there were simply increasing weakness and disability. Unfortunately no blood culture is recorded for Case II. In Case III streptococcus viridans was present intra vitam and a blood culture was taken from the heart post mortem and showed also characteristic streptococcus viridans. Both cases showed during their stay in the hospital the usual findings of a septic endocarditis.



Pathologically all three cases are typical vegetative thrombo-endocarditis. It will be noted that there is no characteristic difference post mortem between acute malignant endocarditis and sub-acute bacterial endocarditis, except for the fact that in the case of sub-acute bacterial endocarditis the heart lesions are, as the name implies, in the sub-acute stage and some of the embolic lesions are generally in the healing stage. In Cases I and III the infective process was still active in the uterus, in Case II this had subsided to a considerable degree. However, the exudate from the uterus and vulva still showed streptococci, and with the clear clinical history connecting the endocarditis with the abortion, there seems no question but that it should be considered as a sequel of a postabortal sepsis. In the acute case it will be noted that there was a generalized peritonitis which might well be considered as a direct extension from the uterus. In the sub-acute cases, however, the secondary foci of infection were all such as might well be attributed to the heart lesion. In other words, the endocarditis was apparently the only process of infection resulting from the puerperal sepsis and the lesions throughout the body were secondary to the process in the heart. Without an association of the clinical and necropsy findings, the connection between the abortion and the endocarditis might well be missed in such cases.

Pathologically Cases II and III are interesting quite aside from the connection between the abortion and the endocarditis. Both cases showed lesions of the mitral valve. In

Case III there was in addition to this a mycotic aneurysm at the base of the aortic valve extending through into the right ventricle, involving the tricuspid valve. Mycotic aneurysms are not unusual in bacterial endocarditis, but it is rare to have the tricuspid valve involved by vegetative endocarditis, and still more rare to have it involved by an aneurysm arising on the other side of the heart and passing through the septum. The presence of these vegetations in the right side of the heart explains the occurrence of the hemorrhagic infarctions in the lung found in this case.

These three cases call attention to the fact that endocarditis, whether acute or sub-acute, is pathologically the same condition, the variation in the clinical picture being largely dependent upon the virulence of the infecting organism. The fact that bacterial endocarditis is particularly prone to attack a previously damaged valve, has been emphasized by Libman (2), Herrick (3) and others. In one of the cases presented, there was a healed endocarditis of the valve which preceded the more recent process. In another there was sclerosis of the endocardium, which may have indicated an older endocarditis. It has been generally accepted that in sub-acute bacterial endocarditis the source of infection is not apparent and such "foci of infection" as tonsils, teeth, etc., have been given prominence as source of entry for the infecting organism. The question may well be raised whether in many of the cases the element of time has not obscured an evident source of infection. For example in a case of septic abortion

following the infection in the uterus there is entrance of organisms into the blood stream. If one of the valves of the heart has been damaged by a previous endocarditis, there is a locus of lowered resistance at which the organisms may settle out. If the infection is with streptococcus hemolyticus, the patient may have a typical acute endocarditis septicaemia, if it is streptococcus viridans she may six months later develop a sub-acute bacterial endocarditis, which neither pathologist nor clinician may associate with the abortion.

No attempt is made to assert on the basis of such a small number of cases, what is the frequency with which sub-acute bacterial endocarditis follows an infection of pregnancy. Neither is there any attempt to refute any established beliefs concerning the origin of the infection in other cases of bacterial endocarditis. However, with these cases in which the connection seems well established and recognizing the pathological similarity of the sub-acute forms to the acute forms it seems justifiable to call attention to the possibility that sub-acute, as well as acute bacterial endocarditis may be a frequent complication of puerperal sepsis. If this be so the careful internist in investigating a case of sub-acute bacterial endocarditis occurring in a woman of child-bearing age must consider the possibility of an infection of pregnancy as a possible source for the infecting organisms of the endocarditis. Furthermore the obstetrician who has a case of puerperal infection or infected abortion under his care must

bear in mind the possibility that even though the acute manifestations of the disease are successfully passed there is still the possibility that an endocardial involvement may occur at a later period. The instances cited emphasize the danger of an untreated septic abortion, since all the cases of endocarditis following abortions which have come to our attention had received no medical treatment until the sepsis was well established. It seems quite possible that thorough and prompt removal of the infected focus in the uterus might prevent such cases of delayed endocarditis and even perhaps the cases of more acute endocarditis.

#### SUMMARY

Three additional cases of bacterial endocarditis resulting from uterine infection following abortion are presented. Attention is called to the well-established fact that an acute endocarditis is a frequent and serious complication of puerperal sepsis. One of the cases presented is illustrative of this type of cardiac disease. Sub-acute bacterial endocarditis, while differing clinically in its course, is recognizable as being the same pathological process differing only in stage, the clinical peculiarities being due probably to the type of infecting organism. The other cases illustrate the fact that sub-acute, as well as acute bacterial endocarditis may be a complication of infection following abortion. In these instances the cardiac condition dominates the clinical picture and the connection with the previous abortion is easily overlooked.

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# Familial Glycosuria. Report of a Large Family.

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THE familial occurrence of glycosuria is attracting increasing interest and families displaying this symptom in several members deserve special study. Joslin (1) records a family in which twelve brothers and sisters and two children are thought to have had diabetes. He reports a Jewish family, eight members of which had diabetes. Landis (2) reports a diabetic family in which the disease was present in the five blonde but not in the four brunette children of a diabetic mother. These are striking examples of families in which all of the individuals showing glycosuria are sufferers from diabetes.

Additional large families have been studied in which non-diabetic as well as diabetic glycosuria has been present in several members.\* Holst (3) gives a good bibliography of the Scandinavian literature and reports eleven families in which two or more members displayed glycosuria, the largest number of glycosuric members in a family was eight. The largest number of diabetics in any of these families was four, the remaining members showed a benign glycosuria. In each of ten of these families the

blood sugar reaction of one member was studied after the administration of glucose, two members of the eleventh family were studied in this manner. Hatlehol (4) reports twelve families, members of which showed benign glycosuria, diabetes was present in five of these families. Malmros (5) reports a family in which 12 members showed glycosuria in the absence of any symptoms of disease.

The following report is concerned with the study of a family in which eighteen members show the presence of a reducing substance in the urine in the absence of any symptom of diabetes. Figure 1 shows the family tree designating the affected members. In five members the blood sugar response to glucose administration by mouth has been studied; the resulting curves display in one case the reaction characteristic of mild diabetes mellitus, in two cases the result is typical of renal glycosuria, in two cases of cyclic renal glycosuria, and in thirteen members the type of blood sugar response has not been studied.

The urine specimens from those members of the family whose responses to glucose have not been studied were collected about two hours after the largest meal of the day because such postprandial specimens are the ones most likely to contain glucose.

\*Hjärne (*Acta Med Scandinav* 67, p 422 quoted by Malmros) studied 169 members of 7 families and found glycosuria in 41 members.

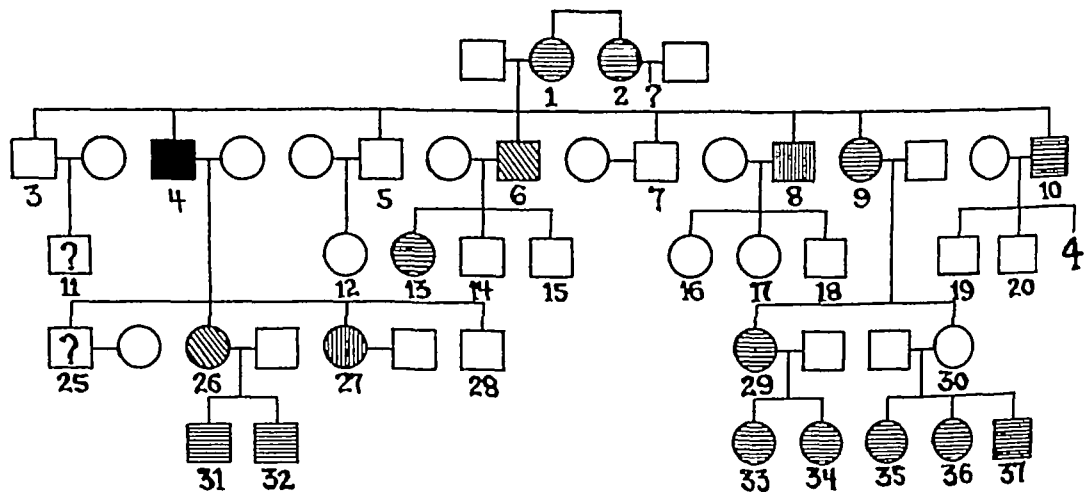


CHART I Family tree Legend The square symbols represent males, the circular symbols represent females The numbers under each symbol correspond to the member number in the text Solid black represents diabetes, diagonal hatching represents renal glycosuria, vertical hatching represents cyclic renal glycosuria horizontal hatching represents glycosuria of an undetermined type, the urine of members represented by plain symbols did not contain glucose The urine of those designated by an interrogation mark has not been tested

The three types of glycosuria mentioned above have the following characteristics —The mild diabetic (6) displays a fasting blood sugar slightly above the normal, accompanied by the presence or absence of sugar in the simultaneous urine specimen Following the administration of glucose by mouth, the blood sugar rises to an abnormally high level, usually reaching the peak of the rise only after an hour's time, accompanied by the appearance of sugar in the urine The blood sugar level then decreases slowly and is still above normal at the end of three hours

With renal glycosuria, the fasting blood sugar level is normal or low, and the simultaneously voided urine contains sugar Following the administration of glucose by mouth, the blood sugar level does not as a rule rise even as high as in the normal individual, the peak of the rise is usually

reached within forty minutes and within two hours the blood sugar has returned to a normal level Varying quantities of sugar are excreted in the urine throughout the test

With cyclic renal glycosuria (7), (8) the fasting blood sugar level is normal and the simultaneously voided urine is sugar-free Following the administration of glucose by mouth, a curve similar to the normal blood sugar response is observed Accompanying the normal rise in the blood sugar the simultaneous urine specimens begin to contain sugar at a blood sugar level, usually between 120 and 140 milligrams per 100 cc of blood, demonstrating a low renal threshold for glucose In other words, glucose appears in the urine only after the ingestion of food or glucose, while in renal glycosuria the urine usually does not become sugar-free even during periods of fasting

REPORT OF FAMILY

The urine specimens from thirteen glycosuric members of the family have been studied by the author, who is indebted to Dr J L Porter for his assistance in discovering glycosuria in several of the members studied. Dr N Peterson and Dr J B H Day determined the presence of a reducing substance in the postprandial urine of other members of the family. It is unfortunate that some members could not be located, and that two declined to submit specimens for examinations.

*Member 1* White female, aged 78, has been obese but is now thin. A recent specimen of urine contained a large amount of reducing substance.

*Member 2* White female, aged 70, a sister of member 1, is said to be thin. A recent urine examination showed a trace of reducing substance.

*Member 4* White male, aged 56, a son of member 1, was seen April 13, 1927. His past history was unimportant except for frequent attacks of epigastric pain. As a young man, these attacks had occasionally required a hypodermic of morphine for relief. He had passed his urine one to three times during the night for fifteen years, but had had no other symptoms of diabetes. He had never weighed more than 145 pounds (65.9 Kg) until he stopped smoking during 1919, following this he had gained weight rapidly and had reached his greatest weight of 207 pounds (94.0 Kg) one month ago. He had exhibited a slight elevation of blood pressure. Sugar had been discovered in his urine during a life insurance examination in 1923. He had not followed a diet and occasional subsequent urine examinations had always shown sugar. His height was 5 feet 6 inches (167.6 cm) and his naked weight was 106 pounds (48.1 Kg). Table 1 shows his blood and urine response to glucose displaying the type of reaction observed in the mild diabetic.

*Member 6* White male, aged 36, a son of member 1, was seen Jan 1, 1927. His past history was unimportant. Starting three years ago he had had nycturia one to three times, some polyuria and marked urgency, during the past year he had not had to pass his urine during the night. He had had no other symptoms of diabetes. Sugar had been discovered in his urine during a life insurance examination in 1916, at which time he had weighed about 150 pounds (68.2 Kg). Later, the sugar had disappeared and he had been able to obtain insurance. His urine has continued to show sugar at times. His greatest weight had been 175 pounds (80.0 Kg), two years ago, his average weight was 160 pounds (72.7 Kg). His height was 5 feet 8¾ inches (174.6 cm) and his naked weight was 155 pounds (70.5 Kg). Table 1 shows his blood sugar curve and urine findings after glucose. The type of response is characteristic of renal glycosuria, although the history of becoming sugar-free at times, suggests cyclic renal glycosuria.

*Member 8* White male, aged 43, a son of member 1, was examined Nov 24 1926. His past history was unimportant. He had been rejected for life insurance during 1916 because of sugar in his urine, at which time he had weighed about 170 pounds (77.3 Kg). He had restricted carbohydrates for six months following this experience and had then been accepted for insurance. There had been no subsequent urine examination. He had passed his urine once or twice during the night for about 10 years, but had had no other symptoms of diabetes. His average weight was 180 pounds (81.4 Kg) and his greatest weight had been 100 pounds (45.4 Kg) one year ago. His height was 5 feet 9½ inches (176.5 cm), and his naked weight was 178 pounds (80.9 Kg). Table 1 shows the blood sugar and urine findings after glucose. The type of reaction is characteristic of the condition described as cyclic renal glycosuria.

*Member 9* White female, a daughter of member 1, is said to be very obese. A recent urine examination showed the presence of a small amount of reducing substance.

TABLE I—GLUCOSE TOLERANCE TEST

Member Number	Member 4			Member 6			Member 8	
	Blood Sugar in mg per 100 cc	Urine Volume	Urine Sugar	Blood Sugar in mg per 100 cc	Urine Volume	Urine Sugar	Blood Sugar in mg per 100 cc	Urine Sugar in grams
Fasting	122	50 cc	0	87	20 cc	Trace	105	0
100 grams glucose as lemonade								
30 min after glucose	200	25 cc	0.3%	133	70 cc	0.8%	171	0.9
1 hour after glucose	250	50 cc	1.3%	111	200 cc	0.3%	135	6.0
2 hours after glucose	190	200 cc	0.8%	99	170 cc	Trace	107	1.2
3 hours after glucose	124	60 cc	0.1%					

*Member 10* White male, aged 60, a son of member 1, weighs 210 pounds (95.5 Kg) and is 5 feet 8 inches (172.7 cm) tall, a reducing substance has been found in his urine by several physicians over a period of years

*Member 13* White female, aged 13, a daughter of member 6, and a granddaughter of member 1, has a small amount of reducing substance in her urine after a meal

*Member 26* White female, aged 21, a daughter of member 4, and a granddaughter of member 1, was seen Feb. 4, 1925, during the early weeks of her second pregnancy. Sugar had first been found in her urine during the early weeks of her first pregnancy, Oct. 21, 1922, starvation for three days and subsequent restriction of diet had not rendered the urine sugar-free. Her greatest weight had been 115 pounds (52.6 Kg) during 1922. Her average weight was 107 pounds (48.6 Kg). She had never had any symptoms of diabetes. Her height was 5 feet 2 inches (157.5 cm) and her naked weight was 101 pounds (45.8 Kg). The blood and urine response to glucose, determined March 6, 1925, is shown in Table 2, taken from a report of respiration studies of renal glycosuria by Paullin (9). During the remainder of the second pregnancy, the puerperium, nursing period and subsequently, this patient's glucose excretion was studied and reported by Bowcock and Greene (10). On Nov. 7, 1928, a 24 hour specimen of urine, volume 1200 cc, contained 35 grams of glucose. This patient writes that she is in good health and weighs 109 pounds (50.0 Kg).

*Member 27* White female, aged 28, a daughter of member 4, and a granddaughter of member 1, was seen Nov. 7, 1928. The past history was unimportant. She had had no symptoms of diabetes and had had nocturia only during her menstrual periods. Her greatest weight had been 125 pounds (56.8 Kg) 10 years ago, her average weight was 105 pounds (47.7 Kg). I had found 0.1 per cent sugar in a single specimen of urine during November 1926. During June 1927 I examined urine passed two hours after a large meal. This specimen contained 3.0 per cent sugar. The urine was dextro-

rotary in the polaroscope and was fermented by yeast. Her height was 4 feet 10 inches (147.3 cm) and her naked weight was 100 pounds (45.5 Kg). Table 3 shows the blood and urine response characteristic of cyclic renal glycosuria following the ingestion of glucose.

*Member 29* White female, aged 33, is a daughter of member 9, and a granddaughter of member 1. Her height is 5 feet 2 inches (157.5 cm) and her weight is 158 pounds (71.8 Kg). On Nov. 17, 1928, a specimen of urine passed after a meal contained a small amount of reducing substance. On Nov. 25, 1928, a postprandial specimen contained 0.43 per cent glucose. The reducing substance reduced Benedict's and Nylander's solutions and gave a heavy yield of osazone crystals with phenylhydrazine.

*Member 31* White male, aged 5 years 6 mos, a son of member 26, and a great grandson of member 1, weighed 6 pounds 4 ounces at birth (2.8 Kg). When one year ten months old, I examined a specimen of his urine which contained 0.1 per cent dextrorotary reducing substance, three subsequent examinations showed a trace of reducing substance on one occasion, and none at the other examinations. On Nov. 9, 1928 he was 3 feet 7½ inches (115 Kg) tall, and weighed 45 pounds (20.5 Kg). A specimen of urine collected two hours after a meal contained 0.23 per cent sugar. The urine gave reduction of Benedict's and Nylander's reagents and yielded an osazone with phenylhydrazine. This child is in good health.

*Member 32* White male, aged 3 years 2 mos, a son of member 26, and a great grandson of member 1, weighed 7 pounds (3.2 Kg) at birth. Except for a mild degree of rickets he has had good health. A specimen of urine at the age of four months gave no reduction of Benedict's solution. On Nov. 9, 1928 his height was 3 feet 1½ inch (92.7 cm) and his weight was 33 pounds (15.0 Kg). A specimen of urine passed two hours after a meal gave slight but definite reduction of Benedict's and Nylander's solutions and a good yield



TABLE 2—RESPIRATION EXPERIMENTS\* MEMBER 26

	Respira- tory Quotient	Calories per Hour	Rise in Calories per Hour	Calories per Square Meter per Hour		Rise Above Normal, Per Cent	Calories from Carbo- hydrate and Fat		Calories from Carbo- hydrate, Per Cent	Calories from Carbohy- drate	Grams Carbohydrate Utilized		Blood Sugar, Mg per 100 Cc	Urine Sugar, Gm
											Total	Increase		
Basal	0.78	55.4		37.9		—2	47.1		26.3	12.3	3.0		78	+
79 Gm dextrose 45 minutes after	0.87	62.2	6.8	42.6		16.5	52.8		57.5	30.3	7.6	4.6	133	3.5
1½ hours	0.78	59.7	4.3	40.9		11.0	50.7		26.3	13.4	3.3	3	132	2.0
2¼ hours	0.76	56	0.6	38.4		3.5	47.6		19.2	9.2	2.3	—7	100	1.5
Dextrose administration														
Dextrose excreted													79.0 Gm	
													7.0 Gm	
Dextrose metabolized, 10.5 Gm, 14.6 per cent of total													72.0 Gm	

\*Technic as described by Boothby and Sandiford, Tissot gasometer and Haldane gas analysis apparatus The results demonstrate normal utilization of dextrose

TABLE 3—GLUCOSE TOLERANCE TEST

Member 27	Blood Sugar in mg per 100 c c	Urine Volume	Urine Sugar
Fasting	89	15 c c	Negative
100 grams glucose as lemonade			
20 min after glucose	131	11 c c	1 Plus
40 min after glucose	134	45 c c	3 Plus
1 hour after glucose	122	75 c c	3 Plus
2 hours after glucose	105	445 c c	2 Plus
3 hours after glucose	83	220 c c	1 Plus
Total volume urine containing sugar		796 c c	0.38% = 3 gms

of osozone crystals when treated with phenylhydrazine

*Member 33* White female, aged 12, is a daughter of member 29, and a great granddaughter of member 1. Her height is 4 feet 8½ inches (143.5 cm) and her weight is 70 pounds (31.8 Kg). At two examinations postprandial specimens of urine have reduced Benedict's and Nylander's solutions and given a good yield of osozone crystals.

*Member 34* White female, aged 4, is a daughter of member 29, and a great granddaughter of member 1. Her height is 3 feet 2 inches (96.5 cm) and her weight is 30 pounds (13.6 Kg). On two occasions her postprandial urine has reduced Benedict's and Nylander's solutions, at one examination the quantitative reduction was 0.29 per cent. A heavy yield of crystals was obtained with phenylhydrazine.

*Member 35* White female, aged 7, is a daughter of aglycosuric member 30, (member 30 aged 25, is 5 feet 5½ inches tall and weighs 188½ pounds, a postprandial specimen did not reduce Benedict's solution), and a great granddaughter of member 1. Her height is 4 feet 3 inches (129.5 cm) and her weight is 52 pounds (23.6 Kg). One of two postprandial specimens gave slight reduction of Benedict's and

Nylander's solutions, and a good yield of osozone crystals.

*Member 36* White female, aged 5, a sister of member 35, is 3 feet 7 inches tall (109.2 cm) and weighs 39 pounds (17.7 Kg). Two postprandial urine specimens gave slight reduction of Benedict's and Nylander's solutions and a good yield of osozone crystals.

*Member 37* White female aged 3, a sister of member 35, is 3 feet 2½ inches tall (97.8 cm) and weighs 35 pounds (15.9 Kg). Two postprandial specimens of urine produced definite reduction of Benedict's and Nylander's solutions and yielded osozone crystals after treatment with phenylhydrazine.

## DISCUSSION

In spite of the fact that only one or two postprandial urine specimens from most of the individual members of this family were examined positive reduction was obtained with the urine of eighteen members. This high percentage of positive results (58 per cent) suggests that had specimens been examined at more frequent in-

tervals the strong hereditary trend of this symptom glycosuria, would have been evidenced by a still higher percentage of positive results

As far as could be determined, all members of the family are in comparatively good health, and in none have the classical symptoms of diabetes mellitus been present. The family is remarkable for the fact that it shows no member with typical symptomatic diabetes. The absence of such symptoms, however, does not exclude the presence of mild diabetes, and studies of the blood sugar response to glucose ingestion would probably demonstrate the presence of a mild diabetic type of reaction in some of the asymptomatic adult members besides member 4. The juvenile members have most probably a benign glycosuria. The types of blood sugar and urine response to the ingestion of glucose displayed by the members thus studied, comprise the usual types of reaction noted in such families. There is, in addition to such types, a rarer type of benign glycosuria which may be present in this family. Campbell (11) has described this rare type under the designation of diabetes innocens. The condition is characterized by a low renal threshold, giving rise to the presence of sugar in urine collected simultaneously with a low or normal fasting blood sugar. There are usually no symptoms of diabetes. After food the blood sugar does not exceed the normal postprandial level, while following the ingestion of glucose the blood sugar level increases to the point of a definite hyperglycemia but returns to normal within three hours. No special

dietary restriction is necessary for the well-being of such individuals. Vogelenzang (12) has described two such cases which he classifies as a probable combination of diabetes mellitus and renal glycosuria. Parsons (13) has reported a similar case under the title of "benign glycosuria with hyperglycemia." Holst (14) mentions a further case. Malmros (15) records an example in one of the glycosuric families, and Paullin and Bowcock (16) have made a detailed study of a similar case with special threshold studies in a patient who was unaware of any other cases of glycosuria in his family.

Whether or not any of the members of this family will subsequently develop symptomatic diabetes is problematical. Holst (3) and many others are of the opinion that a transition from benign non-diabetic glycosuria to true diabetes seldom, if ever, occurs. Malmros (17) after studying the reaction of such glycosuric individuals to insulin and noting that although they developed hypoglycemic symptoms, they did not become sugar-free, concluded that an insufficiency of the pancreas does not cause these forms of glycosuria.

#### SUMMARY

A family is reported, eighteen members of which (representing 58 per cent of the members studied) displayed the presence of a reducing substance in the urine in the absence of other symptoms of diabetes. Glycosuria was first discovered at 22 months in the youngest, and at 78 years in the oldest member. The condition is present in four generations. The blood and urine

response to glucose ingestion has been determined in five members, showing the responses characteristic of mild

diabetes mellitus in one case of cyclic renal glycosuria in two cases, and of renal glycosuria in two cases

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# A Study of Atrophic Cirrhosis of the Liver in Relationship to Syphilis\*

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**T**his paper comprises a review of all cases of cirrhosis of the liver which have occurred in the pathology service of the University of Michigan from the year 1895 through the major part of the year 1925, with the exception of all cases of central cirrhosis biliary cirrhosis, fatty cirrhosis and four cases that could not be definitely classified. Special emphasis is placed upon the concomitant presence of histological evidence of syphilis, either in the liver, or elsewhere in the body.

An exhaustive resumé of the literature was not attempted. Cirrhosis of the liver was described as a hardening of the liver by Vesalius (1514-1564), Harvey, and Morgagni (1). Payne's review (2) of the history of cirrhosis of the liver points out that the earlier workers attributed its cause to the over consumption of water and the excessive use of spirituous liquors among other things. Modern opinion tends to center about two foci. Hawkins (3) would have us believe that atrophic cirrhosis of the liver has no direct etiological relationship to syphilis.

He admits that there may be an indirect or parasymphilitic relationship, but favors chronic alcoholism as the causative agent. Symmers (4) is equally emphatic in his belief that alcohol plays but a minor role in the etiology of atrophic cirrhosis, and that there is at least a certain group of cases of atrophic cirrhosis of the liver in which syphilis is a primary factor. To further minimize the importance of alcohol Symmers states that atrophic cirrhosis of the liver is equally common in Brahmans and Mohammedans, among whom the use of alcohol is religiously forbidden, and further that the long continued administration of alcohol to experimental animals has at no time resulted in the production of atrophic cirrhosis. In a few cases (5) a condition similar to atrophic cirrhosis has been produced in experimental animals by the continued use of sclerotic poisons such as chloroform, in conjunction with certain microorganisms and their toxins. One would expect if Hawkins is correct, that in known chronic alcoholics the incidence of atrophic cirrhosis would be relatively high as compared with all cases of atrophic cirrhosis. This fact is

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largely mitigated by the findings of Symmers (4) and Formad (6). The former found but 3% of cases of atrophic cirrhosis among all autopsies performed on known chronic alcoholics, and the latter found but 6 cases of atrophic cirrhosis among 250 alcoholic patients that came to autopsy.

In studying our cases no attempt has been made to observe the incidence of chronic alcoholism for the reasons that this service includes people from all walks of life, and that many of the histories are too meager in this regard.

With the above exceptions the 2285 autopsies contain 58 cases of atrophic cirrhosis, 16 cases of early cirrhosis which generally have the characteristics suggestive of early atrophic or early syphilitic cirrhosis, 19 cases of syphilitic cirrhosis and 8 cases of Glissonian cirrhosis.

Type	No. of Cases	Percentage
Atrophic	58	0.253
Syphilitic	19	0.083
Early	16	0.070
Glissonian	8	0.035

#### ATROPHIC CIRRHOSIS

In our series of 2285 autopsies atrophic cirrhosis was diagnosed 58 times or 2.5%. This is somewhat higher than the results found by Symmers at Bellevue Hospital, 1.7%. His percentage is based on 4880 autopsies. The 58 cases may be tabulated as follows:

Total No. Cases of Atrophic Cirrhosis	58
No. of Cases of Atrophic Cirrhosis Associated with Histological Lesions of Syphilis	34
Average Age—53 yrs	

Males	29
Average Age—53.8 yrs	
Females	5
Average Age—48.4 yrs	
No. of Cases of Atrophic Cirrhosis not Associated with Lesions of Syphilis	24
Average Age—44.6 yrs	
Males	15
Average Age—43.2 yrs	
Females	9
Average Age—46.6 yrs	

Symmers observed the histological lesions of syphilis in 24 of 84 cases of atrophic cirrhosis, 28.3%. We find this association to be much higher, 34 in 58 cases, 60.3%. The age incidence is seen to run somewhat higher where syphilitic lesions are also present.

In the 34 cases of atrophic cirrhosis associated with syphilis in our series the distribution of cellular evidence of syphilis is as follows:

Lesion	No. of Cases	Percentage
Syphilitic Aortitis*	30*	88.2%
" Orchitis	16	47.0%
" Myocarditis	16	47.0%
" Pancreatitis	12	35.2%
" Adrenitis	12	35.2%
" Hepatitis	9	26.7%
" Leptomeningitis	5	14.7%

\*Lesions occurring less than five times are not recorded.

#### SYPHILITIC CIRRHOSIS

The average age incidence for the 19 cases in this group was found to be 41.1 years. The 12 males averaged 33.8 years which is considerably below the average of 43.0 years for the 7 females. As in atrophic cirrhosis associated with syphilis the incidence of other lesions of syphilis is marked but considerably lower.

Lesion	No of Cases	Percent age
Syphilitic Aortitis	8	42.1%
Myocarditis	7	36.8%
Adrenitis	7	36.8%
Orchitis	6	31.5%
Hepatic Lobatum	6	31.5%
Syphilitic Pancreatitis	5	26.3%

Myocarditis	9	60.6%
Pancreatitis	8	53.3%
Adrenitis	6	40.0%
Orchitis	6	40.0%
Leptomeningitis	5	33.3%

GLISSONIAN CIRRHOSIS

LATENT CIRRHOSIS

As previously stated cases placed in this group, while they favored either the atrophic or syphilitic groups, were too insufficiently developed for positive classification. There were 16 cases. Only one, a male aged 76 years showed no histological evidence of syphilis. The average age of the 15 syphilitics was 50.6 years that of the 7 females was slightly more than half (37.6 yrs) that of the 8 males 60.3 yrs. Lesions of syphilis were present as below

Lesion	No of Cases	Percentage
Syphilitic Aortitis	10	66.6%

Of the 8 clear cut cases of this type of cirrhosis half are found in syphilitics. The average age is 26.5 years. The 3 females average 39 years and the 5 males average 17.2 years. The syphilitic lesions were found in two babies and two middle-aged adults. Old syphilitic lesions occurred in one case orchitis syphilitica fibrosa in another, and congenital syphilis in the two babies.

DISCUSSION AND CONCLUSIONS

If we combine the results of atrophic cirrhosis and early cirrhosis we find

Total No of Cases	Associated with Syphilis		Not Associated with Syphilis	
	Cases	Percentage	Cases	Percentage
74	49	66.6%	25	33.7%

Going a step farther and combining all four types we see

Total No of Cases	Associated with Syphilis		Not Associated with Syphilis	
	Cases	Percentage	Cases	Percentage
101	72	71.2%	29	28.7%

It would seem from the material available in this service that atrophic cirrhosis of the liver is relatively common and that its relationship to syphilis is more pronounced than in other services.

If the syphilitic type of atrophic cirrhosis may be properly combined with the early cirrhotic type the incidence of concomitant lesions of syphilis increases and if all four types may be combined the incidence swells enormously.

The low frequency with which other observers associate atrophic cirrhosis and syphilis may be partly explained upon the relative infrequency with which they diagnose visceral syphilis.

The lack of sufficient data prevents one from being more dogmatic in this matter, but certainly the frequency with which one finds well marked lesions of syphilis so constantly present in such a large percentage of cases of atrophic cirrhosis is of significance.

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# Focal Calcification of Heart Muscle; Case Report

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CALCIUM may be deposited within the cardiac tissue or precipitated directly into the endocardium. Healthy tissue never shows calcium salts deposited. Deposition of the calcium salts in dead or deteriorated tissue, however, is not very uncommon. (1) At first the process consists of a deposition of fine calcium granules, usually phosphates, within the broken up heart muscle fibers. These calcium granules may then coalesce, forming plaques, the latter gradually involving all elements of the heart substance. Scholtz (2) points out that there is no specific cause for this condition but that calcification can occur in the course of any pathological condition, which gradually leads to degeneration of the cardiac muscle fibers of diffuse or localized type. It has not yet been discovered just what rôle pathological conditions of the kidneys plays with respect to its causing interference with calcium excretion and thereby probably increase in the total amount of free calcium salts, aiding the production of pathological calcification such as occurs in the myocardium.

It is the opinion of investigators along this line that the ultimate cause of pathological calcium deposition seems to lie in factors controlling the

calcium tolerance of the cell and in the character of the physio-chemical processes within the individual cells.

Calcium precipitation is an extremely rare condition, and the only two cases which have been reported involved the endocardium only. In both cases the condition was observed in association with calcium metastasis. By metastatic calcification is meant the direct precipitation into apparently normal tissue of the overload of circulating calcium salts produced by extensive bone destruction within the body. The precipitated calcium salts in such cases are occasionally found in the auricles of the heart (also in kidneys, stomach, and lungs). Here too, the endocardium of either right or left auricle is involved. Calcium metastasis could be considered a clinical entity composed of a clinical picture of primary bone destruction, finally superimposed by a second clinical picture somewhat suggestive of acute rheumatism. The real underlying causes of calcium metastasis are still unknown. However, the theory which seems plausible is the main causative factors consist of over-saturation of the circulation with calcium salts associated later on with a breakdown of the mechanism normally provided for excretion of calcium salts,

followed eventually by precipitation of the calcium overload in the places mentioned above

Calcium deposition in the myocardium has been shown by Diemer, Oberndorfer, MacFarland, and Lucas to be the result of extension of the process from the overlying pericardium

A few remarks on pericarditis calcuosa, so-called, or concretio pericarditis, may, therefore, be made here. A review of the literature up to 1923 by Case (3) shows that in only 13 instances has this been recognized in life. Cutler and Sosman (4) have recognized similar calcification in three patients with chronic heart disease.

In one case, the endocardium, pericardium, and myocardium were all involved.

Wells (5) found 4 cases of similar type (pericarditis calcuosa) out of 128 cases of pericardial adhesions from a total 1,000 autopsies.

Calcium deposits in the bundle of His has been reported by Waldorp (6) (1924).

Calcification of the heart may be demonstrated intravital if extensive enough. In such instances one may even succeed in differentiating it from pericardial calcification. Small calcium foci, however, cannot be demonstrated by X-ray during life. Small fine solitary calcium foci within the heart wall may be sometimes overlooked at necropsy as in case herein reported. This may be avoided to some extent by taking X-rays of the removed autopsy specimens whereby very fine calcified areas are localized. Such autopsy radiographic work if carried on systematically will show

that the myocardial calcification is not so very rare as is believed.

X-ray is a very important aid for pathologists in research for small calcium foci and for other changes which cause radio-graphically sufficient differences of tissue density.

Cardiac degeneration due to obliteration of the coronaries with associated calcium deposition have been reported by Burns, Askanazy, and Scholtz (7). Coats and Hedinger described cases (one each) in which myocarditis was due to sepsis. Weichert reported a similar case in which the myocardial damages in which the calcium deposits were found were due to sepsis. Tily described a case of bichloride poisoning resulting in myocardial changes associated with calcification of the heart muscle.

Two cases, one by Roth and another by Siebenmann, have been reported in which there was a combination of metastatic calcification and that due to or associated with myocarditis.

#### CASE REPORT

W. L., colored male, age 47, was admitted to the Memphis General Hospital October 27, 1926 at the request of the Social Service Bureau. As the patient was in the state of coma, it was impossible to get a reliable history. However there was no knowledge of any previous illness until three weeks before the entrance, when his feet and ankles began to swell.

Physical examination showed heart apex 3 cm. outside ant. ax. line. Systolic murmur at the apex and short diastolic murmur down the left sternal border. At the bases of the lungs there were coarse and fine rales with unimpaired resonance.

There was marked edema of the subcutaneous tissue.

Blood pressure 100/150. Temperature 98 pulse 90.

Blood N P N 1625, Creatinine 568,  
Uric acid 842

Total leukocytes—9,450, P N 88% L  
10%, L M 11%

Total erythrocytes—3,590,000 Hb—70%  
(sahl)

The Wassermann test was negative

The urine contained slight trace of albumin and a few red cells

The clinical diagnosis was Malignant Hypertension, Myocardial Insufficiency, Uremic Coma

#### Treatment

Blood was removed twice by reimpuncture October 30, 200 cc were drawn, and 400 cc of Fischer's solution were given intravenously. On November 2, 300 cc of blood were drawn and 500 cc of Fischer's given. 1 ampule of digifolin was given every four hours October 28, 29, 30, then discontinued. Patient was given the Karrell diet beginning November 1st.

The temperature during the following week ranged from 95 to 99.6. The pulse ranged from 86-124. On November 2 the blood pressure dropped from 170/120 and practically all of the oedema had disappeared.

On November 3, the blood showed—NPN 24615, creatinine 727 CO<sub>2</sub> 42 vol per cent. Sugar 0.148 mg.

On November 6 the patient died without having regained consciousness.

#### NECROPSY

The body was that of a negro male well developed but somewhat emaciated, 174 cm in length. There was a conjunctivitis, a pyorrhea, alveolaris, and dental caries. There was also a denuded surface on anterior chest wall, scars and wrinkling over both tibiae. Axillary, inguinal and epitrochlear lymph glands were enlarged. A penile scar, and a large denuded surface over the sacrum, obviously a bed sore were present.

#### INTERNAL EXAMINATION

Peritoneal cavity—There were fibrous adhesions between the omentum and liver and omentum and spleen. There was a mucosal ulceration in ileum just above the cecum, 2-3 cm brownish in color and edges smooth,

not quite perforating. The liver seemed smaller than normal, firmer and was adherent to anterior chest wall. The spleen was adherent to diaphragm and omentum and seemed smaller and firmer than normal.

Pleural cavities. There were dense fibrous adhesions on the right lung between parietal and visceral pleurae, also between the visceral pleura and pericardium and diaphragm. There were 560 cc straw-colored fluid in left pleural cavity. Both lungs were soft and juicy.

Pericardial cavity. There was a fibrous exudate over the entire pericardial cavity. There were large waxy patches on left ventricle and left auricle. The heart was markedly enlarged, apex reaching to 6th interspace, anterior axillary line.

Heart—Weighed 580 grams. The aortic mitral and tricuspid valves were thickened. There were silvery streaks and yellowish areas in the reddish myocardium. The wall of left ventricle was 2½ cm thick.

Aorta. Presented thickened, wrinkled, bark-like appearance.

Lungs. They were soft and juicy on cut surface, serum exuded and cut surfaces presented dark, reddish appearance.

Liver. Weighs 1100 grams. There were dense adhesions. The liver was firmer than normal. There were numerous hard contracted areas throughout. There was a small calcified area on the anterior surface. On cutting the liver was resistant to the knife and presented a reddish color. The gall bladder and ducts were negative.

Spleen. Weighs 11 grams. It was firmer than normal with thickened capsule. It cut with increased resistance, and had a reddish color.

Gastro-intestinal tract. About 4 cm above the cecum there was an ulceration 2x3 cm, edges smooth, brownish, necrotic tissue in center. It involved all coats of intestines, but did not perforate.

Kidneys. Right weighed 65 grams. It was small, firm, contracted and deeply scarred. The capsule was difficult to strip and left a finely granular surface. On cut surface, the cortex was slightly narrowed and the vessels stood up above the surface slightly thickened. The left kidney weighed

100 grams, vessels stood up above the surface, cortex not strikingly narrowed

Brain Some slight edema, otherwise negative

Microscopic Heart section revealed a slight hypertrophy of the myocardium, a rather marked increase of connective tissue. The walls of the blood vessels were thickened. No exudate was seen on the epicardium. There were irregular spotted areas of calcification (see Figure 1)

Pancreas Section revealed a marked increase of inter- and intralobular connective tissue. Blood vessels thickened

Kidneys Section revealed an enormous thickening of the walls of the largest blood vessels. The medium sized blood vessels showed hyperplastic intima. The arterioles were not very markedly thickened. The capillaries were congested and distended with red blood cells. There was marked increase of intertubular connective tissue

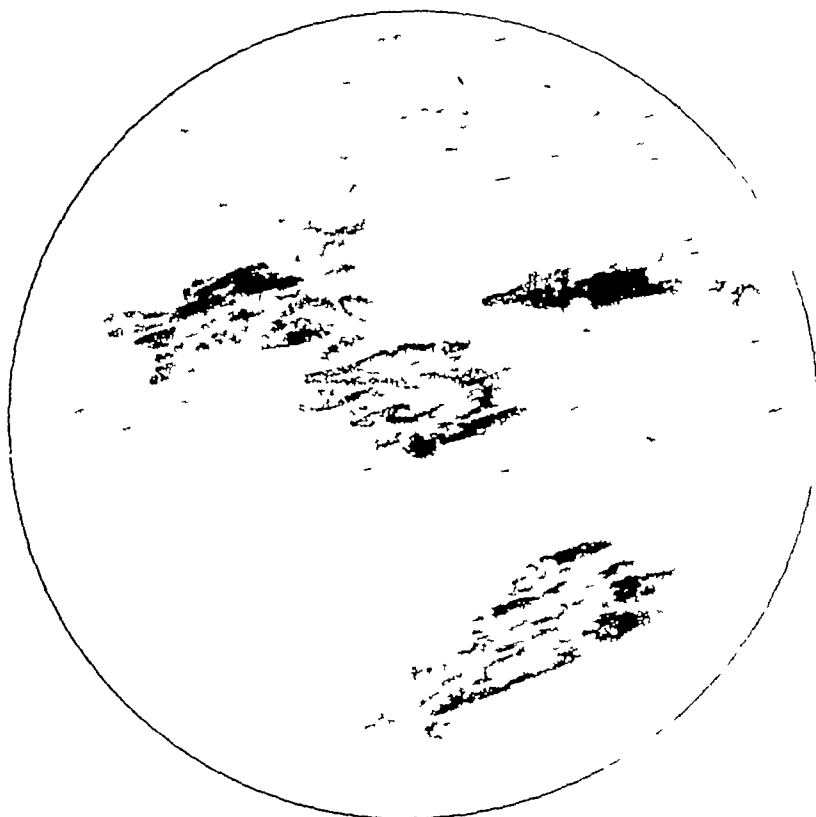


FIG. 1 Microscopic section of cardiac muscle showing focal necrosis and calcification

Lungs Section revealed marked thickening of the walls of the larger blood vessels. There was chronic passive congestion and some emphysema

Liver Section revealed a marked chronic perihepatitis and marked chronic passive congestion

Spleen Section revealed marked chronic congestion, a marked thickening of the walls of the larger blood vessels

and large and small aggregations of small round cells throughout the section. The tubules were atrophied and there were numerous hyaline casts. Some of the glomeruli appeared normal and others showed increase of the endothelial elements of the glomerular tufts, others showed hyaline casts of the glomerular tufts, while still others were atrophied and showed marked fibrosis

brous tissue growing in from the capsule  
to the glomerular tuft

#### Anatomical Diagnosis

Primary Malignant hypertension (gen-  
uine contracted kidney sclerosis and ne-  
phritis) chronic myocarditis with spotted  
calcification, syphilitic mesaortitis, chronic

passive congestion of thoracic and abdom-  
inal viscera, acute fibrinous pericarditis,  
syphilitic ulcer of the ileum

Subsidiary conjunctivitis, dental caries,  
pyorrhea aleolaris, penile scar

Cause of death Malignant hypertension  
with resulting uremia

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# Status Lymphaticus

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THESE is no generally accepted definition of "Status Lymphaticus". This condition clinically is at least in part related to certain constitutional defects variously designated under the terms laryngismus asthma thymicum, constitutio lymphaticus status thymicolymphaticus and others. All of these conditions described at different times by different observers, represent in all likelihood different manifestations and degrees of the same constitutional defect which was first mentioned more than 300 years ago by Felix Plater, who in 1614 reported the sudden death with no apparent cause of a five month's old boy whose most prominent pathologic finding at autopsy was the enlarged thymus. Thus the thymus was made to bear the etiologic burden on the basis of compression of the trachea and adjoining vascular structures and autonomic nerve trunks until the masterful publication in 1858 by Friedleben who established the dictum "Es gibt kein asthma thymicum" and denied that the symptoms were due to pressure. This view was later supported by Paltauf who based his conclusions on a vast amount of pathological material.

Status lymphaticus may be defined as a constitutional defect usually hereditary but occasionally acquired

characterized clinically by definitely peculiar changes in the external configuration, lowered immunity to infection, increased susceptibility to chemical and physical agents and frequently sudden death, physiologically there is an impaired function of the autonomic nervous system, the gonads and adrenals and pathologically, hypoplasia of the cardio-vascular system, arrested development of the chromaffin system, adrenals and pathologically hypoplasia of the lymphoid tissue throughout the body including the lymph follicles of the spleen and hyperplasia or arrested involution of the thymus gland.

Experimental work on status lymphaticus establishes the close interrelation between the thymus and adrenals. In rabbits and rats suprarenalectomy is followed by rapid regeneration and hyperplasia of the thymus and lymphoblastic tissue. It was first demonstrated by Lewis that removal of the suprarenals in rats reduced their resistance at least 400 times. In fact, it was later shown by Scott Tate and Marine and Jaffe that suprarenalectomy in animals produces greater lowering of resistance and hypersusceptibility than any other known experimental procedure. It is interesting to note that the immunologic response is not impaired in as much as the suprarenalectomized

animals retain their capacity to produce antibodies in spite of their lowered resistance. Thus as observed by Tanabe, cases of status lymphaticus in the Japanese army, while manifesting violent reactions to usual doses of typhoid vaccine showed no impairment in their titre of agglutinin production.

The fact that too much emphasis has in the past been placed on the thymus in the etiological role is responsible for the diversity of opinion in the interpretation of status lymphaticus and indeed as recently as 1927 it was asserted by Greenwood and Wood that the term status lymphaticus is a medical myth. Such an unfortunate assertion appears all the more inconsistent to one who has spent any time in the dead house and observed the constant pathologic anatomy of this condition. Status lymphaticus is certainly a distinct pathological entity and to a certain extent also a distinct clinical entity. The thymus plays only a secondary part in the picture and its size depends on the stage or degree of the lymphoplastic reaction at the time.

A clearer conception of the role of the thymus in this condition is hardly possible until more is known of the physiology of the gland. I have reason to believe that the thymic cells are really lymphocytes and that the gland is essentially a lymphoblastic structure. The thymus increases rapidly in weight to the beginning of the third year, remaining stationary until the seventh year when it increases slightly and declines about the eleventh year. At the age of puberty the gland begins to undergo a progressive involution or

atrophy. I am not in accord with the prevalent view that the thymus disappears completely after middle age. In 800 autopsies on individuals past 45 I have observed evidence of glandular remains by histological examination of the anterior mediastinal pad of fat in 20 per cent of subjects in the majority of whom there was no naked eye evidence of thymic remnants.

That the thymus gland begins its permanent involution with sexual maturity is evidence of the close interrelation with the sex glands as well as the other endocrine structures, notably the thyroid and adrenal. It is interesting to note that during the involutionary stage there is regeneration of reticular cells, thymic cells and Hassall's corpuscles, but regeneration cannot keep pace with the involution process except in pathological involution due to infections, intoxications and X-ray exposure, where regeneration may be rapid and complete.

That the thymus has an internal secretion has not been proved. Rather are most inclined to regard it as a lymphoid structure. It has been experimentally established that thymectomy is not followed by important symptoms and that the organ is in all likelihood not essential to life. Its most important contribution is in the nutrition and growth up to the time of sexual maturity, particularly in the development of the bony system. Thus the outstanding effects of experimental thymectomy are referable to the calcium metabolism and deficient ossification. Some attribute to the gland an ability to form antibodies and a detoxicating function (Barbara).

In the relation to the hemopoietic system the thymus like the other lymphoid structures is an important source of lymphocytes and possibly also of eosinophils. In all likelihood it has no bearing on red cell formation.

Interrelation of the thymus with the glands of internal secretion is seen in the effects of castration, suprarenal-ectomy and thyroparathyroidectomy. While removal of the sex glands does not stimulate the thymus to growth it certainly inhibits its involution. Removal of the suprarenals not only prevents involution but also stimulates regeneration. The thyroid gland on the other hand appears experimentally to have an opposite effect since thyroidectomy reduces the growth of the thymus and hastens involution.

Pathologically, the picture of active status lymphaticus is a very definite one. The thymus is enlarged and the microscopic picture depends upon the age of the individual. The medulla shows invariably lymphoid hyperplasia while the cortex may be sclerotic. An eighteen months' old male child upon whom I performed a necropsy following sudden death from violent dyspnea and cyanosis presented a relatively huge thymus which weighed 86.5 grams. Symmers states that in the large series of necropsies at Bellevue Hospital the thymus in typical status lymphaticus averaged 25 grams. The spleen is usually enlarged, sometimes palpably so; the Malpighian follicles are increased in number and size and endothelial elements are occasionally hyperplastic. While there is no demonstrable enlargement of the superficial regional lymph nodes, the lingual and faucial

tonsils and naso-pharyngeal lymphoid tissue are markedly hyperplastic and there is definite hyperplasia of the intra-thoracic and abdominal nodes. Peyer's patches and solitary lymph nodes of the intestine. Collections of lymphoid cells are found in the viscera, particularly the liver. The thyroid is likely to be enlarged and the suprarenal bodies, particularly the medullary substance and extra-glandular chromaffin tissue show hypoplasia. The cardio-vascular system is underdeveloped; the vessels narrow and the walls thin and delicate, lacking elastic tissue and deficient in muscle tissue. Myocardial degeneration, hemorrhages and atheromatosis are prone to supervene. The osseous system shows evidence of impaired calcification and in younger subjects rickets is often associated.

In the recessive types the thymus has been practically entirely replaced by fat and the hyperplastic lymphoid structures show atrophy with sclerotic changes depending upon the stage of involution. The skeletal changes and body configuration of course remain unmodified.

Clinically the children are well nourished, gracefully formed; the skin is marble-like and velvety and the hair is fine and silky. In adults too the skin is pale and delicate; the facial and axillary hairs are scanty; there is very little or no hair on the chest and in the male the abdominal hair is absent and the distribution of the pubic hair resembles that in the female. The thighs are gracefully arched, the waist narrow and external genitalia small. In the female the usual graceful lines are exaggerated and the



avillae contain fat pads with little or no hair. Most of the cases I have seen in females have been blondes.

There is usually a lymphocytosis, hypotension and hypoglycemia. The coagulation time is prolonged. I have never failed to find the lingual tonsils hypertrophied and this is particularly valuable, as it offers an important sign when one is examining a subject who has had a tonsillectomy.

Children mature slowly and secondary sex characteristics are delayed, the musculature is flabby and there is lack of resistance to fatigue and infection. While sudden death sometimes occurs and dramatically so, most cases are probably well able to withstand traumatism and to overcome infection.

The pathogenesis of status lymphaticus is not clear. The condition is obviously congenital although there is no evidence that it is hereditary. Infections in early life probably play an important part.

The actual cause of death in this condition is by no means clear. Many deny that mechanical pressure of an enlarged thymus can itself be responsible. Schule has shown that it requires a weight of 1000 grams to actually close an infant's trachea. In the baby with the huge thymus whose necropsy I have referred to, the gland covered the entire right heart and was adherent to the pericardium. The anatomic signs were those of asphyxia. It is difficult to ignore not alone the possibility of compression of the vessels and right heart but also the influence, particularly in a stage of acute swelling, on encroachment of the thoracic inlet and the effect of pres-

sure on the vagi and recurrent laryngeal nerves with subsequent spasm of the glottis.

In adults the cause of death must be sought for elsewhere. None of the many expounded theories is in itself acceptable. To state that the condition is a hypersusceptibility to physical and chemical agents is no etiologic elucidation. Some state that it is a constitutional defect with increased vagus tone, insufficient chromaffin tissue and inherent weakness of the sympathetic system. Others, notably Symmers, believe that anaphylaxis plays an important part and that sensitization and shock result from the liberation of certain nucleoproteids from the massive and widespread necrosis of the centers of the germinal follicles. It is likely that all of these factors combine to contribute to the final outcome. In the sudden so-called thymic deaths of infants, one is reminded of the pathology in the experimental anaphylactic deaths of animals. I have observed the marked fluidity of the blood, the dilated right heart, the cerebral edema with scattered minute brain hemorrhages, the congestion of the viscera especially the lungs and the petechial hemorrhages of the visceral pleura, epicardium and peritoneum. In adult subjects, the majority of deaths are due to the failure of the inherently weak cardiovascular system. Thus in a number of necropsies on steel mill workers, six of which manifested anatomic signs of status lymphaticus, five showed degenerative myocardial changes with cardiac dilatation and one a thirty-two year old Lithuanian, died suddenly with rupture of a small aneurysm.

of the anterior communicating artery of the circle of Willis. The hypoadrenal state is known experimentally to increase the susceptibility to shock and infection and in its relation to the effect on disturbing the harmonious balance of the endocrine system with the frequently resulting hypoglycemia which occurs in the human subject of this disease one must consider an existing autonomic imbalance with inevitable disturbance of the metabolism.

*Medicolegal Considerations*—Great importance attaches to status lymphaticus in legal medicine, particularly in the matter of sudden death. This was first recognized by the Vienna school of pathologists, notably by Paltauf and Kolisko. Among 5652 autopsies in Bellevue Hospital, Symmers recognized 457 cases of which most were active, some recessive and others partial. It must be remembered that in later years the thymus and lymphoid tissues atrophy. In a review of 2012 necropsies of my own I find recorded in the anatomic diagnosis, status lymphaticus either active or recessive, 180 times. It is to be noted that status lymphaticus will be more often recorded in a series of necropsies in a medical examiner's or coroner's service than in a routine hospital postmortem service, in virtue of the fact that the former is more likely to deal with cases of sudden death and suicides. Many of the subjects of status are mentally deficient and manifest evidence of nervous and mental disease. Thus Bartels observed in an analysis of 122 cases of suicide that anatomic evidence of status was constantly present. Ohlmacher found definite

signs of status in the great majority of fatal cases of epilepsy.

In infancy, many cases of sudden and unexpected death terminating with rapidly increasing dyspnea or cardiac failure, reveal at autopsy that the thymus is much enlarged and the evidence is not altogether conclusive that death can be attributed solely to mechanical pressure on the trachea or great vessels. In adult life, death is more frequently referable to the complications following the hypoplasia of the cardiovascular system. The small heart and narrow aorta with the delicately thin vessel walls are subject to functional disorders, inflammatory lesions, aneurysmal dilation and rupture. Thus we have the sudden and unusual deaths in bathers, or after insignificant trauma or following the careless administration of foreign protein or other substances intravenously. Necropsy records show that a large proportion of rapidly fatal cases of infectious diseases are subjects of status lymphaticus. Subjects with generalized Hodgkins disease usually show anatomic signs of status and many of the endocrinopathies are associated with status in various ways. Hypoplasia of the genitals is common and the bodily configuration has many of the features of pituitary adiposogenital dystrophy.

The case of the young chorus girl twenty-one years old is an example of the marked hypoplastic state of the vessels in this condition and emphasizes the importance of status lymphaticus in legal medicine. It appears that this girl while walking with a escort engaged in an argument whereupon he pushed her vehemently

and she fell to the side-walk, becoming unconscious and dying before the arrival of medical aid. The necropsy of this beautiful blonde showed the smooth pale marble-like skin, silky hair, total absence of body hair except a scanty amount over the pubes and very little over the two distinct fatty axillary pads. The breasts were small, the waist extremely narrow and the pelvis extremely wide with flaring ilia and gracefully arched thighs. The lymphoid tissue was everywhere hyperplastic, the thymus weighed 24.5 grams, the spleen was enlarged and presented huge Malpighian follicles which showed histologically, necrotic centers. Peyer's patches were large thickened swollen masses of lymphoid tissue and the solitary follicles were prominent. The adrenals were small and showed intramedullary hemorrhagic infiltration. The heart was unusually small, the myocardium flabby and the aorta was thin, inelastic and actually no larger in caliber than the small finger. The vessels at the base of the brain were collapsed, narrow, actually the thickness of tissue paper and upon immersion in water it was interesting to see multiple small thin walled aneurysmal sacs, one of which had ruptured with fatal hemorrhage.

#### *Summary and Clinical Significance*

—It has been the purpose of this paper to bring out the practical clinical aspects of status lymphaticus. Only too often one hears expressions from apparently scientific clinicians, to the effect that status lymphaticus does not exist in fact and that the term is used by many, mostly pathologists and occasionally clinicians, to mask their ignorance in certain clinical states and

more particularly in ascribing to it the cause of death where the actual cause is otherwise obscure. It has been my experience that such expressions emanate from men who rarely, if ever, visit the postmortem room. Such unfounded opinions are easily impressed upon the minds of the younger clinical associates. While most of our younger men are well trained in the practical aspects of clinical laboratory procedure, it is extremely difficult to detect any active interest in postmortem activities. The average interne breathes a sigh of relief after he has completed his attendance at the compulsory number of necropsies. Many a postmortem is performed with only the pathologist and the pathological intern present and this in spite of the fact that the necropsy is announced and advertised on the bulletin board several hours before the postmortem is undertaken. It should be the duty of the chiefs of service to set an example by attending all postmortems and thereby stimulating the proper scientific attitude and habits of the younger men.

There is another group of clinicians who while recognizing the pathological status of this condition, express the opinion that status lymphaticus is entirely a pathological entity and can never be recognized during life. When one observes these cases on the post-mortem table again and again, the constant pathologic findings are so pathognomonic as to make an indelible impression. With a visual picture of the anatomic defects and pathological changes in these subjects and keeping in mind those outwardly discernible characteristics already

enumerated, the changes in skin texture the configuration, the lymphoid hyperplasia (as for example the tonsils and more particularly the lingual tonsils) that can be detected by thorough inspection, the hypotension, the often associated though slight mental peculiarities, the relative lymphocytosis, the hypocalcemia, the hypoglycemia a possible history of rickets in early life, the susceptibility to repeated infection, etc., the clinical recognition is no longer a difficult task

Most of the cases do not die from trivial traumatism or minor operations and in fact this is a rare occurrence. By far, most of them attain maturity and as time goes on, present certain symptoms which can in part at least be explained by the inherent constitutional hypoplastic state. When the clinician has all these facts in mind he does not fail to look for

these anatomic signs, he studies the cardio-vascular response, he studies the blood count and blood chemical values with particular reference to sugar and calcium, he orders a metabolism determination and makes other clinical tests to detect any pathological change in the endocrine physiology, as for example, the adrenal response with the Goetsch test. Knowing the tendency toward cardio-vascular hypoplasia, he can caution the subject against undue physical or emotional stress productive of sudden blood pressure changes which are unsafe for a delicate thin walled vascular system. The data enables him to advise X-ray therapy, calcium administration, dietary considerations and certain endocrine products to fit the individual case, as for example, parathyroid, thyroid, pituitary, adrenal substance or sex glands either singly or in combination,

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# Two Cases of Cardiovascular Anomaly\*

## I Vegetative Pulmonary Endarteritis Complicating Persistent Ductus, II Hypoplasia of Aorta

By NEWELL W. PHILPOTT, M.D., C.M., *Chicago, Illinois*

**S**TUDY of congenital cardiac disease offers much of interest and constantly affords many fascinating problems. It is a well established fact that congenital cardiac defects act as a predisposing factor in the occurrence of infectious heart disease. Cardiac anomalies, especially those of the non-cyanotic group, such as defects in the interventricular septum, bicuspid semilunar valves, and patent ductus arteriosus are commonly the site of infective processes. In a series of 656 cardiac anomalies collected by Abbott the total incidence of inflammatory heart disease was 129 cases or 19.6 per cent, of which 96 cases were in the non-cyanotic group and 39 in the cyanotic group. The first case which is now being discussed is classified in the non-cyanotic group and is complicated by inflammatory heart disease.

### CASE No. I

Our first case illustrates clearly the condition of vegetative pulmonary endarteritis in association with a persistent ductus Botalli and superimposed upon an already damaged vessel

wall. The literature records twenty-three cases of patent ductus arteriosus complicated by an infective endarteritis, situated at the pulmonary opening of the ductus and in the adjacent portions of the pulmonary artery. Of these, twenty show an accompanying valvular endocarditis affecting one or more of the heart valves. In only three (Krzyszowski, 1902, Hamilton and Abbott, 1914, Schlaepfer, 1926) were the heart valves intact with the inflammatory process restricted to the pulmonary artery and the ductus arteriosus. This present case makes the fourth on record of this rare condition.

### REPORT OF CASE

G. G., aged 6. Weight 33½ lbs. Admitted to the University Hospital 1/24/28.

*Complaints.* Mother states that the child has a bad heart and is in a general run-down condition.

*Present Illness.* The mother dates the illness from July 1927 when the child developed a running right ear. It was thought that this might be complicated by a tonsillitis but the condition was arrested and was cleared up without an operation. The tonsils and adenoids were removed later, August 1927. Due to continued fatigue, anorexia, and loss in weight the child was kept from school starting early in 1928. In the latter part of the same year the child developed breathlessness and

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No. 1. Heart opened to expose the aorta and pulmonary artery. A Aortic cusp. D Opening of widely patent ductus of Botalli at aortic end. P First part of pulmonary artery showing very marked vegetations in the lumen above the cusps. Note. The aortic cusps, aorta and opening of the ductus at the aortic end are absolutely free from any infective process.

November the family doctor informed the parents that the child had a heart condition. For two months previous to admission the child had a hacking cough and lost  $7\frac{1}{2}$  lbs in weight. Abdominal distention also gradually developed.

*Personal History* Child was a full term baby. Delivery was normal, the color and respirations did not appear out of the ordinary. Two years ago, 1925, had measles and chicken pox. The family doctor states that for the past two years the child has had frequent, severe attacks of tonsillitis.

*Family History* Father and mother are both well. The other two children are in excellent health. The mother's blood Wasserman is negative on two occasions. The other members have not been tested. None in the family have been treated for blood disease.

*Physical Examination* The patient is an acutely sick child who gives the appearance of having been ill for some time, and of having lost considerable weight.

*Positive Findings* There are many râles at both lung bases. Pulse rate is 160 per minute. There is a marked enlargement of the heart to the left and a slight enlargement to the right. The left border is in the anterior axillary line. There is a diffuse pulsation over the apical and pulmonary areas. The sounds are rapid and regular throughout. A very loud murmur, systolic in time, is heard best in the second interspace to the left of the sternum. This is transmitted laterally to the axilla and up the vessels on the left side. The abdomen is distended and tympanic. The spleen is markedly enlarged with the lower border two finger breadths below the umbilicus. Liver edge descends four cms below the costal margin. Some tenderness is noted over the abdomen but the child appears generally hypersensitive.

*Laboratory Findings* The urine shows albumin four plus, many casts, a large number of WBC which are mostly lymphocytes and an occasional RBC. The blood hemoglobin is 34%, RBC are 3,400,000, WBC are 17,000 of which 72% are polymorphs.  $\text{CO}_2$  combining power is 28.7%. Blood Wasserman is 4 plus, repeat 2 plus and 4

plus on a third test. Blood culture report is hemolytic streptococci. X-ray reports an area in the second interspace on the left of increased density suggestive of tuberculosis.

*Course* Was rapidly downhill. During her stay in hospital she ran an irregular temperature which gradually became higher and before death reached a peak of 106 degrees. Her pulse raised in direct proportion to her temperature, ranging from 120 to 180 per minute. The respirations gradually became more rapid and death occurred six days after admission on 1/30/28.

*Final Clinical Diagnosis* Septicemia. Congenital syphilis. Endocarditis and pericarditis. Congenital heart (patent ductus arteriosus?). Subacute glomerular nephritis. Secondary anemia. Abscesses in spleen and liver.

The autopsy was performed five hours after death at 9:30 A.M. 1/30/28.

#### PROTOCOL (ABRIDGED)

G. G. Aged 6

*External Examination* Body is that of a female child 111 cms in length. Has a very slight bony frame, and is of the asthenic type. Gives evidence of recent loss in weight. Pupils are dilated with the left larger than the right. The thorax is long and narrow with the intercostal angle much less than a right angle. The abdomen is rounded, boardlike to the touch with a slight bulging of both flanks. The skin is white and free from ulceration or inflammation. There is no clubbing of the fingers or toes. The incisor teeth have saw-like edges similar to the Hutchinson type. Mucous membranes are pale and slightly cyanotic. Edema is present in each ankle region only. There is a thin white coating over the tongue. The hard palate is high and arched. Ears appear normal with no discharge from either side.

*Abdominal Cavity* Contains 172 cc of a definitely purulent fluid which contains many fibrin threads. There are many adhesions between the coils of small and large bowel. There is no obstruction of the lumen of the bowel. The omentum is thickened and bound down to the underlying

adhesions which tear easily. Liver is 8 cms below the ensiform and  $5\frac{1}{2}$  cms below the costal border in the right mid-clavicular line. Spleen extends obliquely below the left costal border for a distance of 7 cms.

*Thoracic Cavity* Left pleural cavity contains 100 cc of thick, yellow, purulent fluid. There are many adhesions from the posterior surface to the thoracic wall. The right pleural cavity contains 30 cc of a turbid fluid which is slightly blood tinged. No adhesions are present on this side. Heart lies transversely in the thoracic cavity, and is definitely enlarged. The apex is behind the 5th rib in the anterior axillary line. The right border is 2 cms to the right of the mid-sternal line. Left lung is collapsed with the lung borders 7 cm apart in the anterior mediastinum. A small amount of thymic tissue is present in the anterior mediastinum.

*Pericardium* There is a slight increase in thickness toward the base. The tension is definitely increased. The sac contains 50 cc of a clear yellow fluid.

*Heart* Measures  $9 \times 7 \times 3\frac{1}{2}$ , weighs 180 gms. Is much larger than the cadaver's right fist. All the cavities contain a large amount of cruor. The apex is formed chiefly by the left ventricle which is in firm rigor. There is an occasional subserous petechial hemorrhage toward the base. On opening the aorta it is noted that the ductus arteriosus is patent with an opening in the arch measuring 4 mm in diameter. It will admit a large probe with ease and the total length is 75 cm.

*Right Heart* Left ventricular wall measures 15 mm and appears markedly hypertrophied. Musculature is light brown with small whitish areas about 2 mm in diameter noted throughout. The endocardium is smooth and shining with exception of the portion in the left auricular appendage corresponding to the attachment of a parietal thrombus. The mitral valve admits the index finger. The cusps are not roughened and appear normal. The aortic valve admits the thumb. No evidence of vegetations or roughening of the cusps is present.

*Right Heart* The right ventricular wall measures 7 mm and also appears hypertro-

phied. The musculature resembles that found on the left side. The endocardium is smooth and shining throughout. The tricuspid valve admits 2 fingers with difficulty. The cusps show no gross pathological lesion. The pulmonary valve admits the thumb with difficulty, the cusps appear normal. The foramen ovale is closed.

*Coronary Vessels* Are patent and appear normal throughout.

*Left Lung* Measures  $12 \times 10 \times 3\frac{1}{2}$  cm, and weight 190 gms. The surface is roughened corresponding to the attachment of the adhesions, and there is a marked thickening of the pleura. The lung is atelectatic throughout. Cut section shows many firm, dark areas raised above the surface which appear to be patches of pneumonia. There is a definite increase of fibrous tissue surrounding the smaller bronchi and bronchioles. The smaller branches of the pulmonary artery, more marked in the lower lobe, show many thrombi of different ages, some are organized while others are of a more recent nature. In some portions the vessel wall shows an aneurysmic dilatation. Many corresponding infarcted areas are present, some of which appear secondarily infected. No tubercles are found.

*Right Lung* Measures  $14 \times 13 \times 4$  cm, weighs 200 gms. The surface is smooth. Many pneumonic and infarcted areas are also noted on this side especially in the lower lobe. There are also many fibrous bands radiating from the smaller bronchi and bronchioles.

*Pulmonary Vessels* The opening of the ductus arteriosus is 2 cms from the superior border of the pulmonary cusps. On the inferior and lateral wall  $1\frac{1}{2}$  cm from the pulmonary cusps an area 3-2 cm is covered by cauliflower vegetations. These are adherent to the vessel wall and project into the lumen causing a partial obstruction. The opening of the ductus is situated on the opposite side on the superior and lateral aspect.

*Thoracic Aorta* Is normal in size. The intima appears normal throughout. From the opening of the ductus in the arch there is a freshly formed blood clot extending into the lumen of the aorta.





No 2 Left lung with pulmonary artery exposed Note the large, round thrombus in the lumen with a definite saccular aneurysmic dilatation of the vessel at the corresponding point of attachment



No 3 Small branch of pulmonary artery in right lung completely obliterated by an infected thrombus

*Left Kidney* Measures  $10 \times 5 \times 3\frac{1}{2}$  cm, weighs 130 gms. The fibrous capsule strips with ease displaying a markedly congested surface which is smooth. Cut section gives a distinctly boiled appearance with the cortex raised above the surface of the medulla. The pelvis is not distended and there is no gross evidence of a pyelitis. No infarcts are noted.

*Right Kidney* Measures  $11 \times 4 \times 3$  cm, weighs 140 gms. Resembles the left in its gross appearance.

*Female Genitalia* Shows a normal development.

#### MICROSCOPIC FINDINGS

*Cord* Shows early syphilitic meningitis.

*Heart* Subepicardial fat shows serous atrophy. Heart muscle is well developed for age, but there is a degenerative fatty infiltration. Endocardium is thickened but there is a degenerative fatty infiltration. Endocardium is thickened, but there is no fresh process. Valvular endocardium is thickened but there are no vegetations.

*Aorta* Over the base there is a proliferative pericarditis. Higher in the aorta, at the isthmus, there are definite evidences of syphilis, the lesions being of some stranding,—perivascular infiltrations and fibrosis with sclerosis of the media and intima and an older thrombosis on the wall.

*Pulmonary Artery* The wall of the ductus arteriosus and of the pulmonary artery shows definite old syphilitic lesions with a superimposed acute streptococcus viridans vegetative endarteritis, with ulceration of the wall and the formation of a mycotic aneurysm filled with an infected thrombus—thrombo-endarteritis purulenta.

*Lungs* Show chronic purulent pleuritis with fibrosis of the pleura. There is a chronic pleuro pneumonia with marked fibrosis of the interlobular septa. Atelectasis is alternated with dilated air-spaces. Large areas of fibrosis are present. There is a chronic purulent bronchitis. All the branches of the pulmonary arteries show an old obliterating endarteritis with thrombosis. On the older partial thrombosis there is a secondary vegetative process with a distinct tendency to suppuration and to the develop-

ment of mycotic aneurysm. Through the lung are numerous hemorrhagic infarcts in various stages.

*Diaphragm* Shows on pleural side an empyema, on the peritoneal side a subacute peritonitis of less degree.

*Spleen* There is an extreme congestion with necrosis of the centers of many of the follicles.

*Gastro-intestinal Tract* There is a proliferative subacute peritonitis. Mucosa shows an atrophic catarrh.

*Pancreas* Shows atrophy but no signs of syphilis.

*Liver* Is a typical nutmeg liver with a localized chronic perihepatitis. There is no evidence of syphilis.

*Kidneys* Show a sub-acute glomerulotubular nephritis. Many glomeruli are in various stages of repair.

*Lymph-nodes* Show hyperplasia with proliferation of the reticulo-endothelium. There are no tubercles.

*Pathological Diagnosis* Mycotic aneurysm of the pulmonary artery opposite the mouth of the patent ductus Botalli (streptococcus viridans infection on an old syphilitic arteritis). Multiple organizing emboli in pulmonary arterial branches with hemorrhagic infarctions. Chronic pleuropneumonia. Atelectasis. Bronchopneumonia. Subacute empyema. Acute syphilitic meningitis of cord. Marked chronic passive congestion of liver and spleen. Sub-acute glomerulotubular nephritis. Diffuse proliferative peritonitis. Marked hyperplastic lymphadenitis.

#### DISCUSSION

*Clinical Findings* From the clinical aspect this case demonstrates very well the condition of persistent ductus Botalli being complicated by an infective process. Before the onset of the fatal illness the child displayed no

definite signs of a congenital heart lesion though she always appeared weak and pale. The last illness was preceded by frequent attacks of tonsillitis, a right-sided otitis media with a questionable involvement of the mastoid region. Other cases on record give histories of a very similar nature. Four have histories of a preceding rheumatic fever, repeated attacks of sore throat were a feature in the case reported by Sommer. Schlaepfer's report states that the onset of the fatal illness was preceded by a bilateral otitis media.

A review of the other cases on record show the physical findings to have a striking likeness. Diagnosis of the patent ductus is made by some or all of the following signs being present —

1—A thrill felt over the pulmonic area

2—Dullness in the upper spaces to the left of the sternum

3—Roentgenray reveals an area of increased density due to increased volume of the pulmonary artery. This is shown in the 2nd left interspace.

4—Accentuated pulmonary second sound

5—A murmur heard best in the pulmonic area and transmitted up and to the left

Our case shows —

1—A diffuse pulsation in the pulmonic and apical regions

2—Enlargement of the heart to the left

3—Pulmonic second sound markedly accentuated

4—Systolic murmur in the pulmonic area and transmitted up and to the left

The infective process is of a subacute nature, the course being progressively downwards. The average duration is from six months to one year. Two cases, Buchwald and Hamilton, lasted only two months while that reported by Boldero extended over a period of two years. The picture is that of a typical blood-stream infection, blood cultures have shown streptococcus viridans, staphylococcus albus, influenza bacillus, and pneumococcus. The present case proved by blood cultures taken before death and at autopsy to be a streptococcus viridans infection.

*Pathological Findings* The picture is typically that of a streptococcus viridans infection superimposed upon an active congenital syphilis. The lungs and pulmonary artery show old syphilitic lesions. Due to lowered resistance and mechanical strain, a vegetative endarteritis developed upon the intima of an already damaged pulmonary artery and ductus. The lungs contain multiple infarcts, abscesses, and areas of chronic pneumonia with an extensive empyema. A secondary peritonitis is present due to an inflammatory extension of the empyema through the diaphragm. The glomerulo-tubular nephritis is typical of that found in streptococcus viridans infections.

There is a definite localization of the vegetative endarteritis to an area in the pulmonary artery opposite the ductus opening and to the ductus wall. The three other cases on record show a very similar localization, those by Schlaepfer and Krzyszkowski have the process strictly confined to that portion of the pulmonary artery at

the ductus arteriosus opening Hamilton's case shows the pulmonary artery likewise involved but, in addition, the process extends along the wall of the ductus

Infarcts in the lungs, spleen, kidneys, intestines, skin and brain are found to be frequent complications Multiple abscesses in the lungs are common Thrombus formations in the smaller branches of the pulmonary artery with aneurysmic dilatations of the vessels, similar to those found in the present case, have been reported by Sachs, Kidd, and Krzyszkowski

This case also demonstrates the fact that the Wasserman reaction on the blood of women during the child-bearing period is often of no significance A mother who has borne one or more children and who is definitely syphilitic frequently has a negative blood Wasserman which will not become positive until she reaches the menopause In this present case the child gives definite evidence of congenital syphilis and had a positive blood Wasserman on four occasions The mother on two examinations, is negative to the Wasserman test

#### SUMMARY

- 1—The child has congenital syphilis
- 2—Ductus of Botalli is persistent
- 3—At the age of six she develops a streptococcus viridans infection with a vegetative endarteritis of the pulmonary artery There is no accompanying endocarditis
- 4—The illness is of a sub-acute ending fatally after a period of six months
- 5—There are twenty-three cases on

record of patent ductus Botalli associated with a pulmonary endarteritis Only three in addition to the present report have an endarteritis of the pulmonary artery with no accompanying valvular lesion

#### Case No 2

#### Hypoplasia of the Aorta

Hypoplasia of the aorta commonly occurs in conjunction with a certain set of cardiac anomalies These include coarctation of the aorta anomalies of the aortic arch, bicuspid semilunar valves, persistent left superior vena cava and patent foramen ovale For this reason the condition of hypoplasia of the aorta is usually classified with congenital cardiac defects It occurs, however, as an isolated condition not in association with any cardiac anomaly and may be manifested by the aorta and its branches being markedly reduced in size often measuring only  $\frac{1}{3}$  the normal caliber

Much discussion has arisen as to whether this isolated condition is a true congenital cardiac anomaly or whether it is purely a post-natal lack of development Subjects of the thymico-lymphatic constitution possess an aorta which is hypoplastic Usually this hypoplasia is not pronounced but occasionally we find the vessel markedly diminished in size, often suggesting a congenital defect On investigation these cases are found to possess other characteristics common to the thymico-lymphatic constitution such as a hyperplastic thymus generalized lymphoid hyperplasia and hypoplasia of the adrenals The condition of hypoplasia of the aorta

lunar valves persistent left superior with no associated cardiac or circulatory defect is probably a manifestation of a definite constitutional type

### CLINICAL REPORT

Miss A. A., Aged 17

Was admitted to the University Hospital 2-15-28 with the chief complaints of dyspnoea, cyanosis, palpitation, and edema. She has always been delicate. At the age of 8 a swelling was first noted in her neck and at this time, she was not gaining in weight. At the age of 12 a specialist was consulted who prescribed "goitre pills." Shortly after, her symptoms became more marked and the pills were discontinued. When 13 years of age her family doctor found an enlarged heart and a "leaky valve." One year later, 14 years of age, she developed chills and fever. Endocarditis was suspected though the blood culture was negative. In November 1927, aged 16, edema was first noticed. This was accompanied by a slight cyanosis of the lips, fingers, and toes. She was digitalized for the first time in January 1928, one month before admission.

*Past History* Had influenza in 1918. No definite history of rheumatic fever, chorea, or scarlet fever. Had her tonsils removed at the age of four.

*Family History* Nothing to denote syphilis. No history of heart trouble on either side of the family.

*Menstrual History* Began at the age of 14 and were regular until four months ago. Since then have occurred more often and have been more profuse.

*Physical Examination* She is intensely dyspnoic, very cyanotic, propped up in bed, with a constant anxious expression. There is a marked pulsation of the neck vessels and the thyroid is enlarged.

*Lungs* Respirations 32 per minute. There is impaired resonance throughout with dullness at both bases. Many crackling râles are heard at both sides.

*Heart* Radial pulse is 104 per minute, weak, but regular. Cardiac dullness extends 12½ cms to the left and 3 cms to the

right of the mid-sternal line. Sounds are rapid, regular, and weak. A harsh systolic and diastolic murmur is heard at the mitral and aortic areas.

*Abdomen* The liver is enlarged and extends two fingerbreadths below the costal margin. There is a slight dullness in both flanks.

*Extremities* Show a massive edema most marked in the lower extremities.

*Laboratory Findings* Urine—albumin is slightly positive with an occasional hyaline and granular cast. Blood exam—95% hgb. R B C—7,000,000. W B C—12,300. Differential is not important. N P N of blood 68.2 mgms. Electrocardiogram shows a marked right ventricular preponderance.

*Course in Hospital* Death occurred two days after admission. Her temperature was always slightly sub-normal. Orthopnea and cyanosis became very marked. A venesection was done and 500 cc of blood withdrawn. This relieved her condition for only a few hours. The patient expired 2/15/28.

### Clinical Diagnosis

- 1 Aortic insufficiency and stenosis
- 2 Mitral insufficiency and stenosis
- 3 Congenital heart (type not specified)
- 4 Polycythemia (secondary)
- 5 Cardiac failure

The autopsy was performed two hours after death.

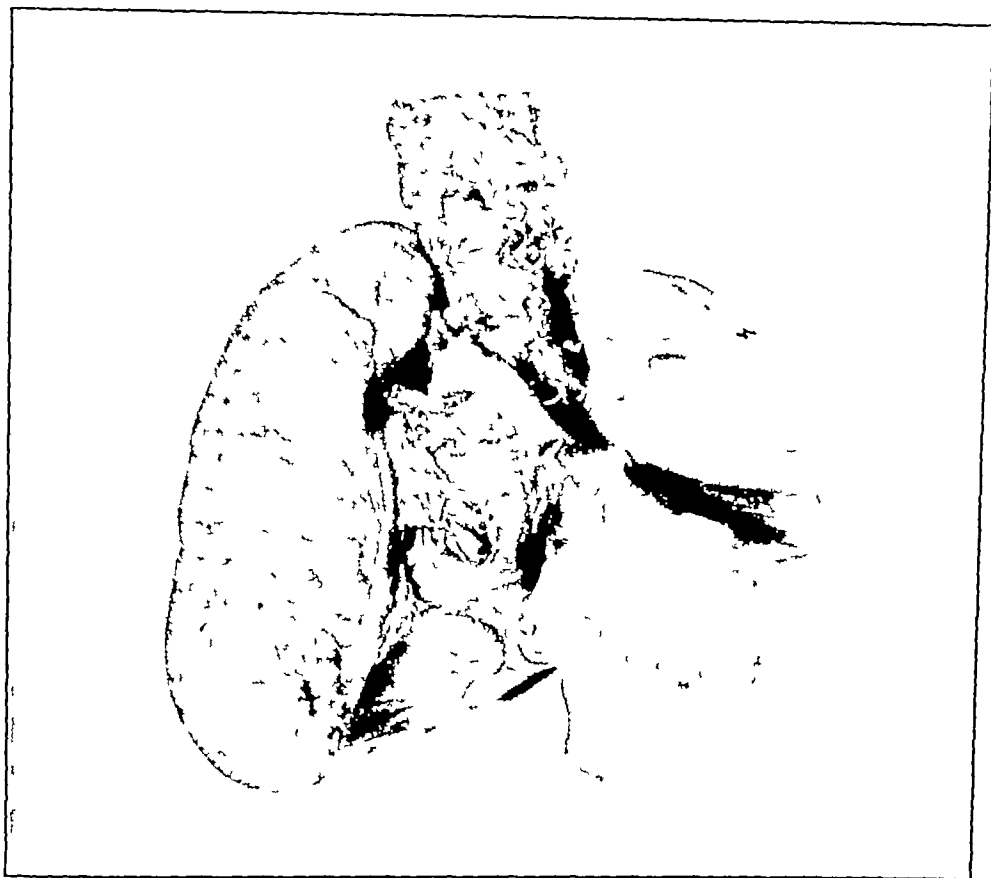
### PROTOCOL ABBREVIATED

Miss A. A., aged 17, 2-15-28

*External Examination* Body is that of a young adult female, 159 cms in length, of a light bony frame. There is a very marked generalized edema. Many small ulcers averaging 5 mm in diameter are present in the skin of the lower extremities. The face, mucous membranes, and extremities show a marked cyanosis, and there is a dark purple hypostasis present in the dependent portions. There is no clubbing of the fingers or toes.

*Abdominal Cavity* Contains 200 cc. of a slightly turbid, yellow fluid.

*Pleural Cavities* Right pleural cavity contains 450 cc of a clear, yellow fluid.



No. 4 Posterior view of thoracic organs, showing the marked hypoplasia of the aorta  
Case 2

The left pleural cavity contains 300 cc of a similar fluid

*Position of Thoracic Organs* On removing the sternum it is noted that the heart is very markedly enlarged with the pericardial sac lying transversely in the thorax. Both lungs are displaced laterally by the enlarged heart. Measurements of the pericardial sac intact are 18-13-8½ cm.

*Anterior Mediastinum* Is entirely filled by the enlarged heart and a hyperplastic thymus.

*Thymus* Extends downward over the anterior surface of the pericardium. The thymic tissue is markedly congested and distinctly hyperplastic.

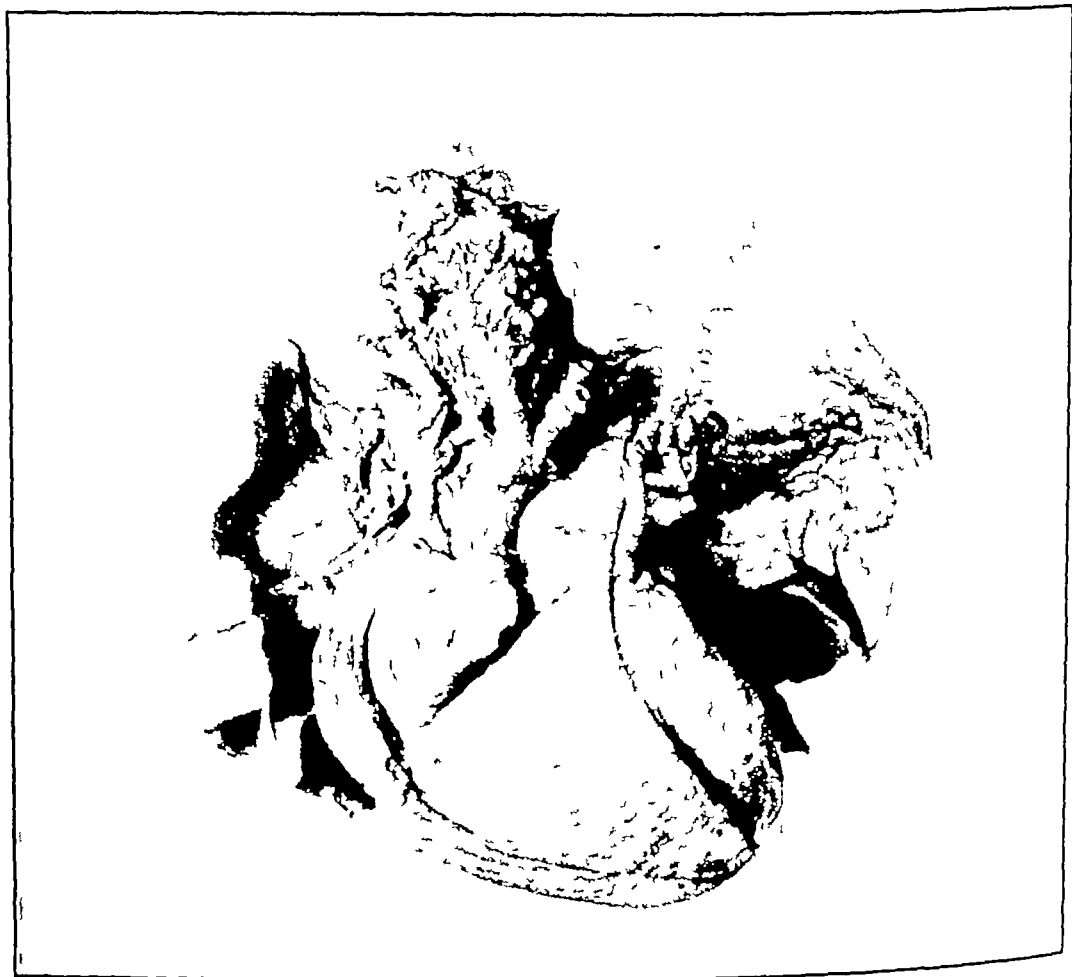
*Pericardium* The wall is not thickened but there is a very definite increase in tension. The sac contains 400 cc of a clear

fluid. In no place is the pericardium adherent to the heart wall.

*Heart* Measures 15 x 11 x 7½ cm. is markedly enlarged. The apex is made up by both ventricles but more so by the right.

*Note* The heart, lungs, and aorta are removed intact and placed in 10% formal. Eight days later a careful dissection was done to observe any abnormal anastomosis of the vessels or any congenital defect which may be present.

*Left Heart* The left ventricular wall measures 14 mm. The musculature appears slightly hypertrophied. No gross areas of fibrosis are noted. The endocardium in the left ventricular cavity is smooth and shining. There is a marked stenosis of the mitral valve with a generalized thickening of the cusps and occasional areas of calcification.



No 5 Lateral view of thoracic organs together with the great branches of the arch as far as the bifurcation Case 2

The ascending portion of the aorta is shown, The much dilated pulmonary artery is shown

fication Only the tip of the forceps can be passed through the opening, the diameter measuring 7 mm In the left auricle the endocardium surrounding the mitral valve is very roughened and deeply congested The left auricular wall averages 3 mm in thickness, and there is a very slight dilatation present The left ventricular cavity is exceptionally small The aortic valve admits the index finger, but the lumen is diminished in size superior to the valve There are three cusps present and the coronary vessels arise from the normal locations

*Right Heart* The right ventricular wall averages 17 mm in thickness, and is markedly hypertrophied No gross areas of fibrosis are noted The endocardium is smooth and shining throughout The tricuspid valve admits three fingers with difficulty, the

edges of the cusps are rolled under and appear slightly thickened, but there is no roughening The right auricle is markedly dilated, with the cavity filled by a large amount of cruor The auricular wall is hypertrophied, measuring 9 mm at its thickest portion The average thickness is 6 mm The pulmonary valve admits three fingers with difficulty, the cusps appear normal The foramen ovale is closed

*Pulmonary Vessels* There is a marked enlargement of the pulmonary artery Superior to the cusps the total diameter is 39 mm with the diameter of the lumen 34 mm Throughout the first portion and the main branches the enlargement is constant The ductus arteriosus is obliterated

*Aorta* This vessel shows a very pronounced hypoplasia throughout its entire

course Superior to the aortic cusps the diameter is 18 mm and at the arch measures 13 mm The size of the vessel remains constant in the descending portion with the diameter at a level of the diaphragm also 13 mm The vessel wall is decreased in thickness, appearing in proportion to the size of the lumen Both iliacs arise from their normal position and are also hypoplastic

All blood vessels are carefully traced and no evidence is found of any anomalous anastomosis The internal mammary artery is not enlarged on either side, the bronchial, pericardial and esophageal branches follow their normal course

*Lungs* There is atelectasis of the lower lobe on both sides with a marked congestion and edema of the remaining portions

*Thyroid* Does not appear increased in size Only a moderate amount of colloid is present

*Adrenals* Are hypoplastic There is a moderate lipoidosis of the cortex and the medulla appears well preserved

*Female Genitals* The uterus and ovaries appear hypoplastic

#### MICROSCOPIC FINDINGS

*Heart* The left auricle shows marked chronic productive endocarditis with marked fibrosis and areas of active infiltration mostly mononuclear in type Mitral valve shows chronic endocarditis with marked fibrosis and calcification with abundant reactive infiltrations, both polynuclear and mononuclear Left ventricle shows old sclerosis of endocardium, atrophy of heart muscle with diffuse fatty degenerative infiltration The right auricle shows marked hypertrophy of wall with fatty degenerative infiltration and very small infiltrations in the myocardium, lymphocytic in character The right ventricle shows moderate subpericardial fatty infiltration, hypertrophy of the wall with diffuse fatty degenerative infiltration and small lymphocytic infiltrations There is a slight sclerosis of the endocardium near the tricuspid valve

*Aorta* Markedly hypoplastic Intima shows early stage of atherosclerosis No aortitis

*Lungs* Marked brown induration and chronic passive congestion Bronchioles are dilated Blood vessels show markedly thickened walls with the lumina very small

*Thyroid* Marked lymphoid hyperplasia Graves' constitution Increase of stroma Colloid fairly abundant Parathyroid included shows no pathology

*Thymus* Atrophic, but showing abundant thymic remains Is an atrophic hyperplastic thymus

*Liver* Marked chronic nutmeg liver with beginning central cirrhosis and marked interlobular cirrhosis Proliferation of small bile ducts in islands

*Adrenals* Very hypoplastic with excessive lipoidosis

*Lymph Nodes* Very marked lymphoid hyperplasia Hyperplasia of reticulo endothelium

*Hemolymph nodes* Show marked congestion of the sinuses, and a most marked lipoidosis of the reticulo-endothelium

*Breasts* Underdeveloped Small ducts resembling male breasts

*Uterus* Slight subepithelial inflammation Endometrium is underdeveloped

*Ovaries* Congestion, cystic follicles, and a small number of corpora fibrosa

#### PATHOLOGICAL DIAGNOSIS

Old sclerosing chronic mitral endocarditis with button-hole stenosis Marked hypoplasia of aorta and iliac arteries Marked dilatation of pulmonary artery Cardiac hypertrophy with right-sided preponderance Dilatation of right heart with relative pulmonary insufficiency Marked brown induration of lungs with areas of atelectasis Marked nutmeg liver with early central and more marked interlobular cirrhosis Extreme congestion of all organs Combined thymico-lymphatic and Graves constitution (marked lymphoid hyperplasia of thyroid atrophic hyperplastic thymus marked hypoplasia of aorta and





No 6 Left ventricle opened showing the stenosis of the mitral orifice Case 2

adrenals generalized lymphoid hyperplasia with exhaustion of germ centers) Marked hyperplasia of hemolymph nodes with angiectatic blood sinuses and marked lipoidosis of the reticulo-endothelium Chromophobe hyperplasia of the pituitary Hypertrophy of renal glomeruli Hypertrophy of islands of Langerhans

### DISCUSSION

This subject is definitely of the thymico-lymphatic constitution with some added characteristics of the Graves' type The marked hypoplasia of the aorta is a manifestation of her constitution, and there are also present many other of the characteristics common to this group The liver shows a combined cirrhosis, the central cirrhosis is of the Pick's disease type while the interlobular cirrhosis is similar to that found in many of the subjects of the Graves' constitution

The mitral endocarditis appears to be an old rheumatic infection Subsequent to the mitral stenosis and sclerosis of the smaller branches of the pulmonary artery, a marked right ventricular preponderance has developed Cyanosis and polycythemia are manifested in the terminal stages

This polycythemia is definitely compensatory Due to the mitral stenosis and marked sclerosis of the smaller pulmonary vessels normal oxygenation of the blood is prevented Development of the polycythemia is very similar to that in Ayerza's disease where there is a sclerosis of the pulmonary vessels On both occasions in hospital the blood count showed the red cells over seven million, the highest count being 7,900,000

Clinically she showed a definite thyroid disturbance which was aggravated by the administration of "goitre pills," probably containing iodine Microscopic findings prove the thyroid to be of the Graves' constitution type showing the effects of too much iodine

To summarize

1—This is a case of marked hypoplasia of the aorta not associated with any cardiac anomaly

2—She is definitely of the thymico-lymphatic constitution

3—The mitral stenosis is caused by a chronic endocarditis of the rheumatic type

4—Due to poor oxygenation of the blood a compensatory polycythemia develops in the terminal stages

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# A Case of Complete Transposition of the Viscera With Electrocardiographic and X-Ray Studies

By AARON E. PARSONNET M.D. F.A.C.P. *Attending physician, Beth Israel Hospital, Newark, New Jersey*

**T**RANSPOSITION of the viscera, although not a rare condition, is interesting. Reports of such cases serve a very useful purpose of putting the physician on guard for these anomalies. To the surgeon and needless to say, to the patient, a timely diagnosis of visceral transposition is obviously of the greatest importance.

This case came under my observation through the courtesy of Dr. Samuel Roth, of Newark, and holds absolutely true to type as proven by physical findings, electrocardiograms, and X-ray studies.

*History.* L. F., aged 35, well developed, overnourished white male, was seen by me on May 30, 1928, with chief complaint of "pain over heart." Past history discloses nothing of importance; measles and several attacks of tonsillitis were the only diseases of childhood. He always enjoyed good

health and never complained of any symptoms referable to the cardio-vascular or respiratory systems. His father has had disease at 63, mother living and well at 65.

*Physical Examination.* The apex was not visible and not palpable but was heard in the fifth interspace inside midline on the right. All heart sounds were clear, well transmitted through entire thorax, regular, and no murmurs, shocks, or thrills could be elicited. Orthodiagram measurements showed the heart to be of normal size, and fluoroscopic examination revealed the dextrocardia clearly. Right and left border configurations were normal in outline. Blood pressure readings were systolic 130 and diastolic 85. The lung fields were essentially clear throughout with minute cardiac dullness over right chest. Spleen could not be palpated on the right but definite liver dullness was present in the left upper quadrant. Under the fluoroscope, typical stomach air bubble seen in right upper abdomen.

The following X-rays were taken on May 6, 1928:—

The electrocardiogram given below shows inversion of the P, QRS, and T waves in the first lead very clearly. All complexes are upright and well formed in second and third leads. These findings are typical of a dextrocardia.

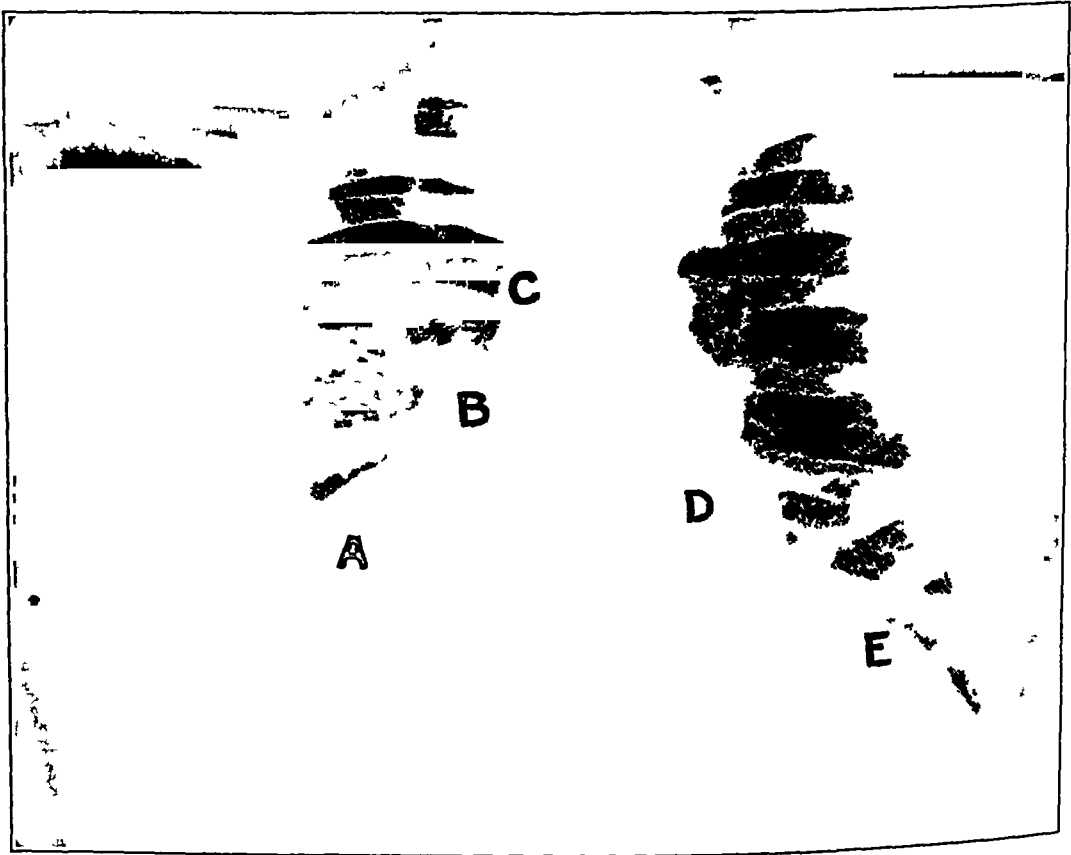


FIG 1 A Left ventricle  
B Left auriculo-pulmonic curve  
C Arch of aorta  
D Right heart  
E Diaphragm

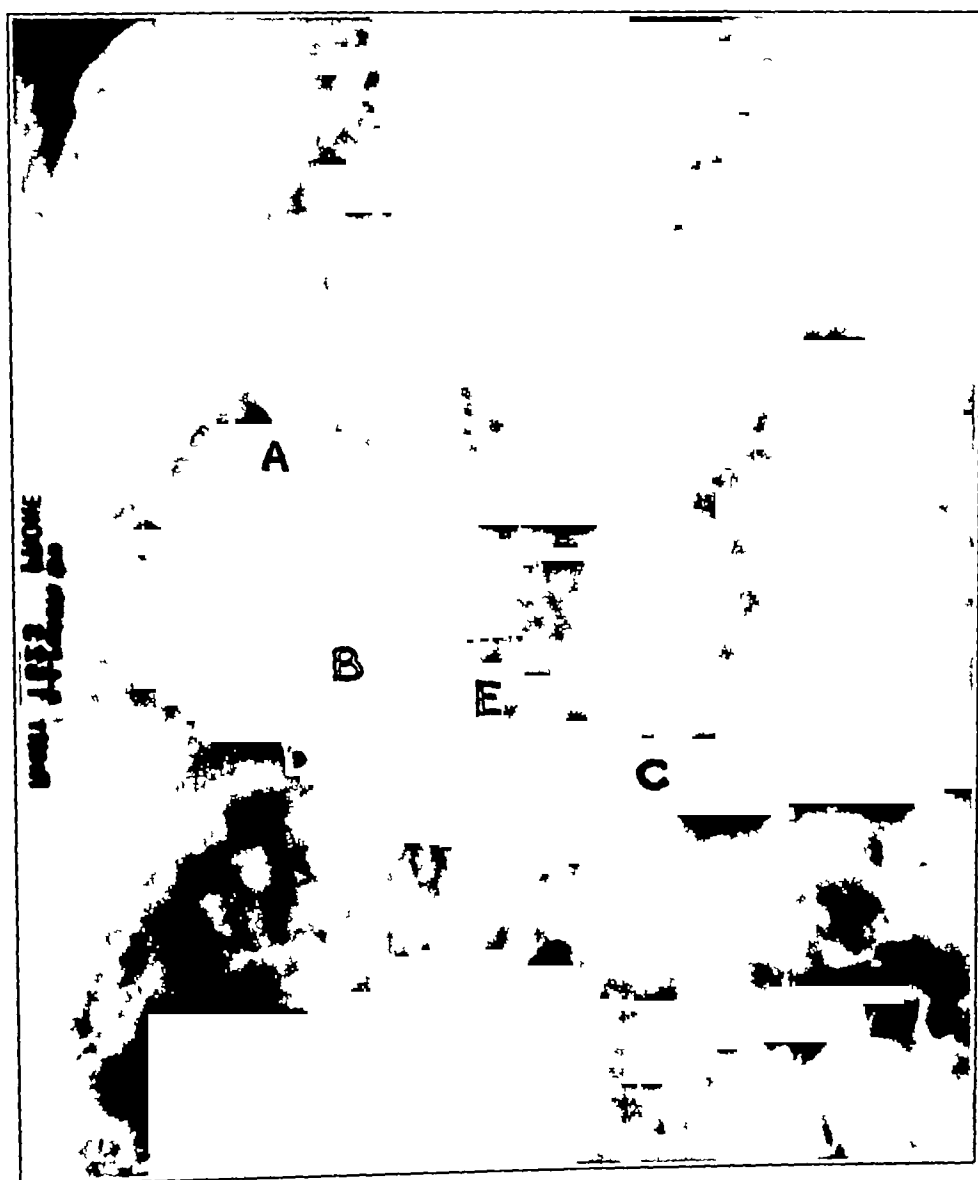


FIG. 2 A Pars cardia  
 B Pars media  
 C Pars pylorica  
 D Greater curvature  
 E Lesser curvature

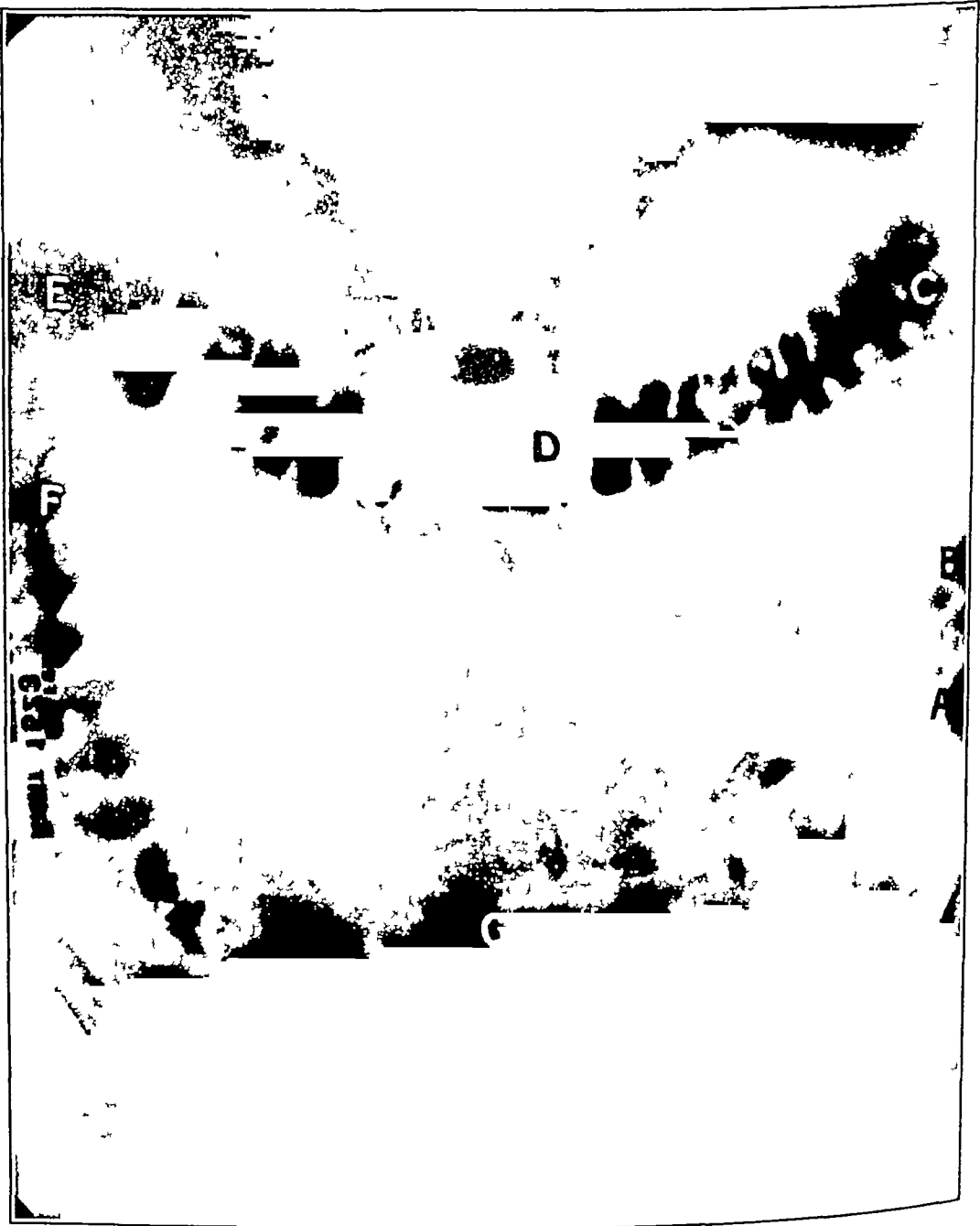


FIG 3 A Caecum  
B Ascending colon  
C Hepatic flexure  
D Transverse colon  
E Splenic flexure  
F Descending colon  
G Sigmoid

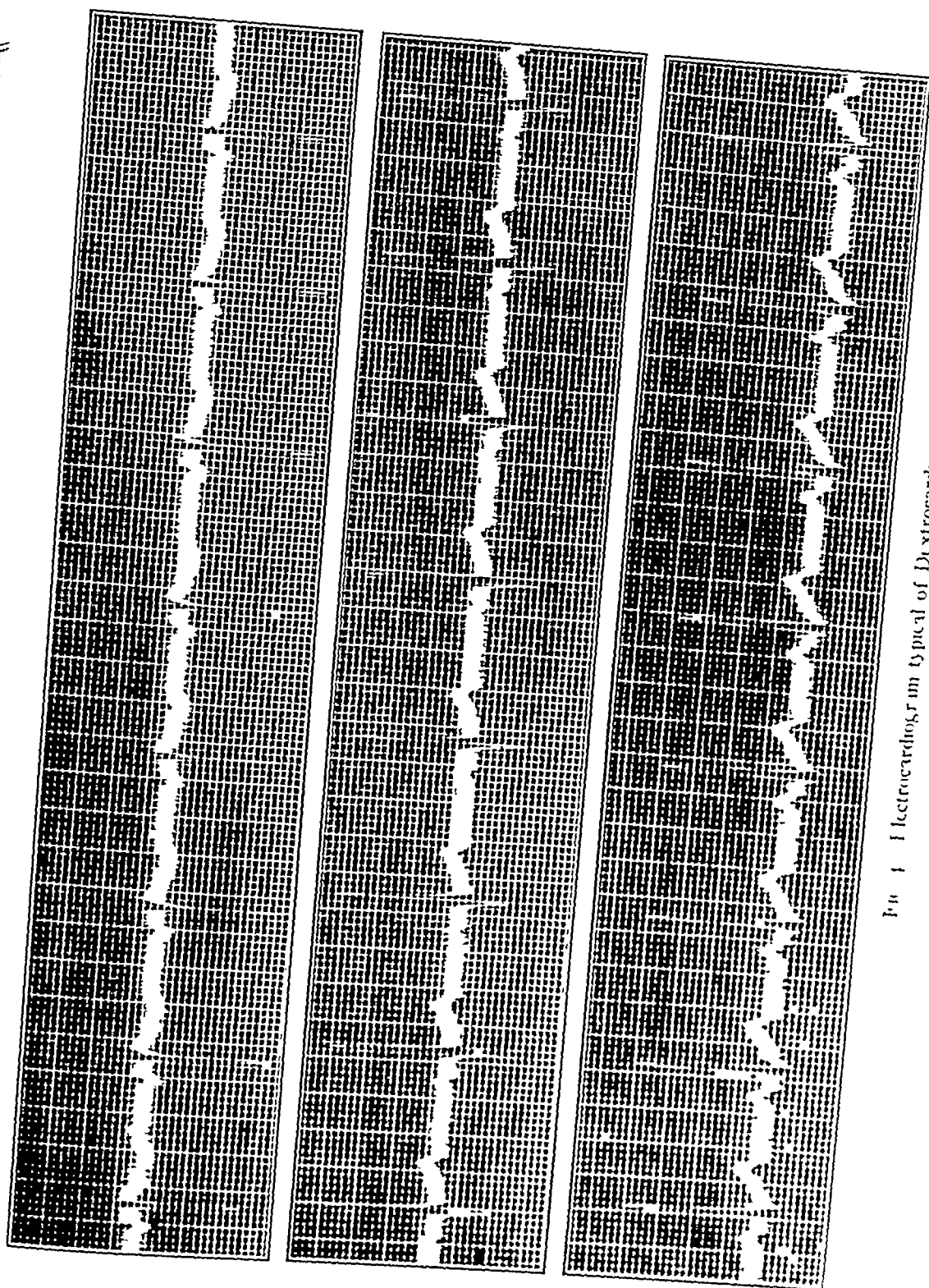


Fig. 1. Electrocardiogram typical of Dextrocardia



## Editorial

### *SYPHILIS AND LIFE INSURANCE*

Karl Vajda of Budapest has an article on "Versicherungsmedizinische Beziehungen der Syphilis" in the number of the *Klinische Wochenschrift* for January 29, 1929, that deserves careful reading and thoughtful attention from every internist who is in any capacity concerned with life insurance examinations. Syphilis has always been one of the most disputed problems of insurance medicine, for two reasons, one, because of the fact that the applicant for insurance, having passed through the active stages of his syphilis, does not mention it to the examiner, and two because it is extremely difficult often impossible in most cases to make a diagnosis of latent syphilis in the short time allotted to the medical examination. This diagnosis can be much more easily made under the conditions of private practice. In making the insurance examination the examiner has only a relatively short time for his examination so he is forced to omit all methods that may be regarded as burdensome to the candidate. Thus the taking of a Wassermann is attended by difficulties, and a spinal reaction is in the majority of cases not even thought of. Although we have made numerous advances in the diagnosis of syphilis since the discovery of the spirochete,

yet few of these advances are utilized in life insurance examinations to the advantage of the life insurance companies. Syphilis remains today as it was thirty years ago, one of the most easily missed conditions in life insurance examinations. There is no criterion of complete healing of the disease. A previous syphilis is and remains a menacing danger to life insurance. The latest statistics show that the mortality ofluetics exceeds that of non-luetics by 68 per cent. This means that for every one hundred cases of death within a given age-class for all insured there are 168 deaths inluetics of the same age class. The examination of the various disease groups shows that the excess mortality ofluetics over that of malignant neoplasms is 60 per cent over that of renal diseases 64 per cent over diseases of the gastrointestinal tract 116 per cent, over suicide 122 per cent over that of apoplexy 128 per cent and over that of the group of psychopathic diseases 145 per cent. And this is far from being the whole truth! For in these statistics only those candidates are regarded as luetics who have acknowledged their condition to the examiner. How great the number of those who keep silent as to those who have no knowledge that they possess a latent syphilis. We must assume that the excess mortality of theluetics is very much greater.

than indicated by these statistics. We must not forget in this connection that a candidate with manifest syphilis is never accepted for life insurance. Only such luetic individuals who have had syphilis and have passed through a corresponding treatment for the same and show no symptoms, so that they are regarded by the examiner as completely healed are accepted. Herein lies the greatest feature of the syphilis problem. There is at the present time no doubt existing in any one's mind that the *Spirochaeta pallida* is the cause of syphilis, and although many facts relating to the biology of this organism are still unsettled we do know that it can reproduce in the human body for many decades without producing any symptoms. During this period of latency the patient may enjoy perfectly sound health, and the physician on the most careful examination can find nothing pathologic. Suddenly in the heart, in the aorta, the central nervous system, in the liver in the kidney the spirochetes begin their deadly work. Involuntarily we must think of that expression of the great clinician Gerhardt, "Die Syphilis schliesst wohl Waffenstillstand, aber niemals Frieden." The great tragedy of it all is that all of these manifestations of this infection are in very many cases diagnosed when all too late for treatment. In the first row stands progressive paralysis as the true horror of life insurance companies. Although the various statistics show that only 2-3 per cent of luetics become paralytic this percentage would hold only for the insurance companies in case every luetic individual would be in-

sured. It is actually much higher among insured luetics, because mental workers rather than laborers fall victims to paralysis. The percentage of cases of progressive paralysis among the insured luetics is 10-12 per cent. Tabes dorsalis is less important than progressive paralysis from the standpoint of the insurance company, in that this form of syphilis leads to death usually only after several decades. Only a few years ago both of these diseases were regarded as meta-luetic or parasymphilitic. Today both are recognized as being nothing else but syphilis of the brain and syphilis of the spinal cord. A similar important role is played by syphilis in the etiology of arteriosclerosis particularly coronary sclerosis, aortic insufficiency, aortic aneurysm atrophy hepatitis flava, aortitis and myocarditis. Further, there is a large group of diseases to which syphilitics are especially predisposed, such as neurasthenia, gout, diabetes mellitus and cancer. Blaschko has made the observation that he has never seen a cancer of the tongue case that did not have a positive Wassermann. Birsony has called attention to the very high percentage of carcinoma of the uterus occurring in luetic women at the Budapest Frauenklinik. The fearful sequelae of syphilis are well shown in the statistics compiled by Pilz and Matruschek of 4134 officers of the general army who had acquired syphilis between 1880-1900. These officers had been treated 4-5 weeks with an injection cure and thereafter dismissed with a potassium iodide prescription. The following year they were again examined and it signs of

syphilis were still present no one troubled himself as to whether the affected officer should have further treatment or not. The mortality statistics of these officers in the next 12 years showed that 132 died of brain syphilis, 193 of progressive paralysis, 113 of tabes dorsalis, 80 of different psychoses, 17 of aortic aneurysm, 101 of organic heart lesions, 44 of apoplexy, 40 of tertiary syphilis, 147 of pulmonary tuberculosis, and 60 committed suicide. While tuberculosis does not belong to the so-called meta-luetic diseases, it is an old experience that syphilis predisposes to tuberculosis, and that a mild infection often becomes very malignant following an intercurrent infection with syphilis. In the case of those officers who took only one injection cure not less than 23 per cent became paralytic, while of those whose treatment extended over two years only 3.23 per cent developed paralysis, while in those who had a four years' treatment there was not a single case. Eleven years ago Blaschko estimated that there were 40 per cent of the male inhabitants and 19 per cent of the female of the city of Hamburg infected with syphilis, in Berlin 37 per cent male and 17 per cent of the female population. Yet at this time in both of these cities only 3 per cent of the candidates for life insurance acknowledged that they had had the disease. It is easy, therefore, to understand the concern of the life insurance companies in the earlier and more certain diagnosis of latent syphilis. If every luetic candidate for life insurance would acknowledge that he had had the disease the whole problem becomes reduced to a mat-

ter of financial calculation. Given the excessive mortality rate of the luetic in any age class the increase in premium rate can be easily adjusted. But most of the luetics are silent as to their infection. Some actually do not know that they have had the disease, and some have totally forgotten. There remains, therefore, nothing for the examiner but to make the most painstaking examination possible, many Wassermanns should be taken, and if these are repeatedly negative a bacteriologic and serologic examination of the spinal fluid should be made. But it must not be forgotten that a positive Wassermann does not always indicate syphilis, or that a negative Wassermann does not mean the absence of syphilis. The problem, therefore, cannot be settled in a certain number of cases. It is to be remembered also that very often it is the mildest forms of the disease that terminate in progressive paralysis or tabes. Of great importance in the history are the facts of a childless marriage, or repeated abortions on the part of the wife. Also various conditions of the eye are very suspicious. Syphilis plays a much more important role in the etiology of iritis and retinitis than is suspected, a parenchymatous keratitis is probably always syphilitic, likewise chorio-retinitis pigmentosa and optic atrophy. Further of great importance are single neurasthenic disturbances. Since the candidates are always silent as to these subjective symptoms the objective manifestations of the earliest symptoms of progressive paralysis and tabes are of greatest importance. The concentration power of the candidate

should be fully tested, the inability of the incipient case of paralysis to repeat rapidly simple movements of the eyes, tongue and hand should be noted. Here belong also apraxia and dyspraxia facialis-hypoglossus paresis tremors of tongue and lips, and above all the pupillary changes. Anisokoria is one of the earliest symptoms occurring many years before the loss of pupillary reflex. The loss of the pupil reflex is in 98 per cent of cases a symptom of tabes or paralysis. In concluding his observations Vajda states that after 4-5 years of scientific treatment insurance may be given a luetic without especial increase of premium. But the number of such candidates is so very small compared to those imperfectly treated that the greatest care must be taken in regard to the latter class. In this group he would give no insurance to any one with active clinical symptoms until perfectly treated. A half year after the end of such treatment in the total absence of symptoms insurance for a period of 15-20 years can be given at normal premium rates. After that period insurance can be continued at a small increase of premium. In case there are no symptoms and the candidate has been well treated without symptoms for the last two years, he may be accepted at normal rates for 15-20 years if five years has passed since the infection. If ten years have elapsed since the infection then a slight increase of the premium is justified. Because of the action of the International Serum Conference in regard to the evaluation of the negative and positive Wassermann reaction

Vajda can no longer support the views of v d Berghs that in the case of a negative Wassermann in the candidate for life insurance a small increase of premium should be made, and in the case of a positive reaction a greater increase in the premium rate.

### THE MEETING IN BOSTON

From the large number of letters coming in to the Editor's office it would seem that a large attendance is already assured for the Boston Clinical Week. This augurs most promisingly for the success of this meeting. The Boston men have prepared a fine program. Especially attractive is the clinical program which ensures a high grade of clinics suitable for the postgraduate. Attention has been given to the criticisms of the clinics presented at the last two Clinical Weeks to the effect that these clinics were of an order suitable to senior students but not of a postgraduate quality and flavor. The medical visitor to Boston may be assured that all of the clinics presented there are by trained clinicians who have had postgraduate experience and that the material and the presentation will be worthy of the reputation for high-class postgraduate work which Boston has always enjoyed. In addition to those given by the local men clinics will be presented by members of the College from other cities, whose reputation for giving postgraduate work of the highest class is well-known. As far as the medical value of the Boston Clinical Week is concerned its success is assured through its program. It behooves the Fellows to

Associates of the College to take advantage of this opportunity for social and intellectual refreshment. As to the other aspects of the meeting in Boston very little can be said in addition to what the special articles on Boston already published in the College News Notes have offered. The historic interest of the city is so great, so interwoven with the history of America, that the visitor to Boston for the first time will have his time wholly filled for him if he does nothing but visit the great historic buildings and scenes which make of the city such a unique object lesson for early American history. The city portion of Boston with its mingling of historic buildings and business blocks has an English atmosphere—the vis-

itor may easily fancy himself to be in London in some of the vistas seen through narrow passage-ways and streets. To the acquainted visitor the art collections of Boston offer much, to the botanist and gardener the Arnold Arboretum is an unfailing joy and interest, to the musician the opportunity for hearing the Orchestra is an enticement, for the educator there is Harvard and the Institute, for the book-lover there is the Widener collection, in fact Boston offers something especially choice in every line of human interest. So then, come to Boston, and plan to take advantage of the many great opportunities, both medical and cultural, that the holding of the Clinical Week in this interesting city makes available to you.

## Abstracts

*Syphilitic Heart Disease with Failure* By DUDLEY C. SMITH and RAYMOND D. KIMBROUGH (The Southern Medical Journal, August, 1928, page 634)

This analysis is based on the study of fifty-six cases admitted to the University of Virginia Hospital between July, 1923 and July, 1927. All of the cases had heart failure and were diagnosed syphilis of the heart or aorta. Syphilis was considered the primary etiological factor, this was proved by autopsy in some of the cases, but in most of them the diagnosis was based on clinical and laboratory data. The cases of heart disease showing what was considered an incidental syphilitic infection and those in which it was thought to be of secondary importance were discarded. In addition to the usual medical investigation consisting of history, physical examination and routine laboratory methods thirty-four of the patients had electrocardiograms, forty-two were X-rayed and eight were autopsied. Of the fifty-six cases, thirty-nine (69.6 per cent) were negroes, and seventeen (30.4 per cent) were whites. The proportion of negro syphilitic patients to white syphilitic patients in the hospital and out-patient departments was 3 to 2. From these figures it is estimated that syphilitic heart disease occurred one and one-half times as frequently in syphilitic negroes as in syphilitic whites. The average age of the negro patients in this group of admission was 45.8 years as compared with 52.6 years for the white patients. The greater incidence and the earlier occurrence in the negro indicates an increased susceptibility in this race to cardiovascular involvement from syphilis. There were forty-nine male and seven female patients. Fourteen were farmers, twenty were laborers and the occupations of all the others required considerable physical exertion. The average age at admission was 47.7 years. There was a positive history of

a genital sore in twenty-five cases. The average interval in these from the initial infection to the onset of failure was twenty-two years. The shortest interval was eight years, the longest forty-one years. Only one case gave a history of early cutaneous lesions. This would seem to confirm the idea expressed by Brown and Pearce in their law of inverse proportion, that severe late visceral involvement occurs more often following mild early reactions. This finding is paralleled by the well substantiated observation that neurosyphilis is relatively less frequent in those patients who have had severe skin symptoms. It is impossible to say whether this is due to different strains of organisms or to an individual visceral susceptibility. Tabulation of the initial symptoms gave the following results: dyspnea 29 (51 per cent), heart pain 10 (18 per cent), palpitation 10 (18 per cent), substernal pain 3 (5 per cent), weakness 3 (5 per cent), cough 2 (4 per cent), vertigo 2 (4 per cent), headache 1 (2 per cent) and dyspepsia 1 (2 per cent). Some showed more than one initial symptom. Other early symptoms were: edema 25 (50 per cent), dyspnea 14 (25 per cent), heart pain 12 (21 per cent), cough 12 (21 per cent), palpitation 11 (20 per cent), vertigo 10 (18 per cent), weakness 9 (16 per cent), substernal pain 4 (7 per cent), dyspepsia 3 (5 per cent), choking sensation 3 (4 per cent), nervousness 2 (4 per cent), sleep starts 2 (4 per cent), headaches, convulsions, insomnia, cyanosis, hoarseness and buzzing sound in heart 1 each. Functionally twenty-five cases presented both congestive and anginal failure, thirty showed congestive failure alone and one anginal failure alone. The abnormal structural findings based on physical examination, tele-roentgenograms, fluoroscopic examination and autopsies were as follows: cardiac hypertrophy 51 (91 per cent), aortic regurgitation 47 (84 per cent), mitral regurgitation 46 (82 per cent), aortic stenosis 45 (80 per cent), mitral stenosis 44 (79 per cent), coronary artery disease 43 (77 per cent), aortic aneurysm 42 (75 per cent), mitral aneurysm 41 (73 per cent), aortic valve disease 40 (71 per cent), mitral valve disease 39 (69 per cent), aortic valve stenosis 38 (68 per cent), mitral valve stenosis 37 (66 per cent), aortic valve regurgitation 36 (64 per cent), mitral valve regurgitation 35 (62 per cent), aortic valve stenosis and regurgitation 34 (60 per cent), mitral valve stenosis and regurgitation 33 (59 per cent), aortic valve regurgitation and stenosis 32 (57 per cent), mitral valve regurgitation and stenosis 31 (55 per cent), aortic valve stenosis, regurgitation and aneurysm 30 (54 per cent), mitral valve stenosis, regurgitation and aneurysm 29 (52 per cent), aortic valve regurgitation, stenosis and aneurysm 28 (50 per cent), mitral valve regurgitation, stenosis and aneurysm 27 (48 per cent), aortic valve stenosis, regurgitation and aneurysm 26 (47 per cent), mitral valve stenosis, regurgitation and aneurysm 25 (45 per cent), aortic valve regurgitation, stenosis and aneurysm 24 (43 per cent), mitral valve regurgitation, stenosis and aneurysm 23 (41 per cent), aortic valve stenosis, regurgitation and aneurysm 22 (40 per cent), mitral valve stenosis, regurgitation and aneurysm 21 (38 per cent), aortic valve regurgitation, stenosis and aneurysm 20 (36 per cent), mitral valve regurgitation, stenosis and aneurysm 19 (34 per cent), aortic valve stenosis, regurgitation and aneurysm 18 (32 per cent), mitral valve stenosis, regurgitation and aneurysm 17 (31 per cent), aortic valve regurgitation, stenosis and aneurysm 16 (30 per cent), mitral valve stenosis, regurgitation and aneurysm 15 (28 per cent), aortic valve regurgitation, stenosis and aneurysm 14 (27 per cent), mitral valve stenosis, regurgitation and aneurysm 13 (26 per cent), aortic valve regurgitation, stenosis and aneurysm 12 (24 per cent), mitral valve stenosis, regurgitation and aneurysm 11 (23 per cent), aortic valve regurgitation, stenosis and aneurysm 10 (22 per cent), mitral valve stenosis, regurgitation and aneurysm 9 (21 per cent), aortic valve regurgitation, stenosis and aneurysm 8 (20 per cent), mitral valve stenosis, regurgitation and aneurysm 7 (19 per cent), aortic valve regurgitation, stenosis and aneurysm 6 (18 per cent), mitral valve stenosis, regurgitation and aneurysm 5 (17 per cent), aortic valve regurgitation, stenosis and aneurysm 4 (16 per cent), mitral valve stenosis, regurgitation and aneurysm 3 (15 per cent), aortic valve regurgitation, stenosis and aneurysm 2 (14 per cent), mitral valve stenosis, regurgitation and aneurysm 1 (13 per cent), aortic valve regurgitation, stenosis and aneurysm 0 (12 per cent), mitral valve stenosis, regurgitation and aneurysm 0 (11 per cent), aortic valve regurgitation, stenosis and aneurysm 0 (10 per cent), mitral valve stenosis, regurgitation and aneurysm 0 (9 per cent), aortic valve regurgitation, stenosis and aneurysm 0 (8 per cent), mitral valve stenosis, regurgitation and aneurysm 0 (7 per cent), aortic valve regurgitation, stenosis and aneurysm 0 (6 per cent), mitral valve stenosis, regurgitation and aneurysm 0 (5 per cent), aortic valve regurgitation, stenosis and aneurysm 0 (4 per cent), mitral valve stenosis, regurgitation and aneurysm 0 (3 per cent), aortic valve regurgitation, stenosis and aneurysm 0 (2 per cent), mitral valve stenosis, regurgitation and aneurysm 0 (1 per cent), aortic valve regurgitation, stenosis and aneurysm 0 (0 per cent).

"Classification of the Anemias and Discussion of the Most Important Types," by William C. Colbert, Memphis, Tennessee

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Sir Humphrey Rolleston, Regius Professor of Physic, University of Cambridge, England, delivered on March 20-21, the first course of lectures at Johns Hopkins University under the William Sydney Thayer (Fellow) and Susan Read Thayer, Lectureship in Clinical Medicine. This lectureship was endowed by friends of Dr. Thayer last year when the American Medical Association met in Washington and made Dr. Thayer President-Elect of that organization.

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At the Minneapolis Session of The American Medical Association, diagnostic clinics were conducted by the following Fellows of The College on June 11

Dr. W. McKim Marriott, St. Paul, "Pediatrics",

Dr. F. M. Pottenger, Monrovia, "Pulmonary Tuberculosis and Bronchiectasis",

Dr. Elliott P. Joslin, Boston, "Diabetes",

Dr. John H. Musser, New Orleans, "Pernicious Anemia"

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Dr. Charles A. Reye (Fellow), Charleston, is President of the West Virginia State Medical Association

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Dr. Edward J. G. Beardsley (Fellow), Philadelphia, recently addressed the Ohio County Medical Society, Wheeling, West Virginia, on "Conditions that Simulate Pneumonia"

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Dr. David Riesman (Fellow), of Philadelphia, was awarded the degree of Doctor of Science at the commencement exercises of Franklin and Marshall College at Lancaster, Pa., on June 5

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Dr. Waller S. Leathers (Fellow), Nashville, Professor of Preventive Medicine and Associate Dean of the Medical School of Vanderbilt University, was appointed Dean of said school by the Board of Trustees of that institution at their meeting on June 12

Dr. Leathers succeeds Dr. G. Canby Robinson who recently resigned to become Director of the medical center of Cornell University and the New York Hospital in New York City. Dr. Leathers was formerly Dean of the Medical School of the University of Mississippi and Executive Officer of the State Board of Health

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Harvard University at its annual Commencement on June 21, conferred the Honorary Degree of Doctor of Science on Dr. George R. Minot (Fellow), of Boston.

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Dr. Hubert Work (Fellow), Secretary of the Interior in the Cabinet of President Coolidge, has been appointed Chairman of the Republican National Committee, which will manage the campaign of Secretary Hoover and Senator Curtis, the Presidential and Vice-Presidential nominees. Dr. Work announced that he would retire as a member of the Coolidge Cabinet

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Dr. James M. Anders (Master), of Philadelphia, was honored by the Degree of Doctor of Science at the Commencement Exercises of the University of Pennsylvania

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## OBITUARY

"Valdemar Sillo, M.D., of 353 West 57th Street, New York, N. Y., was born in 1867 and graduated as physician from the Eclectic Medical College in the City of New York in 1902. He practiced medicine in the City of New York and was well liked by his patients and colleagues. He was an honest straightforward man, a competent physician and a true friend. Gout and angina pectoris carried him off from this world on October 29th, 1927.

"We express our sympathy to the widow and the near relatives. Dr. Valdemar Sillo will live in the memory of his friends as an example of good fellowship"

## YEAR BOOK SUPPLEMENT

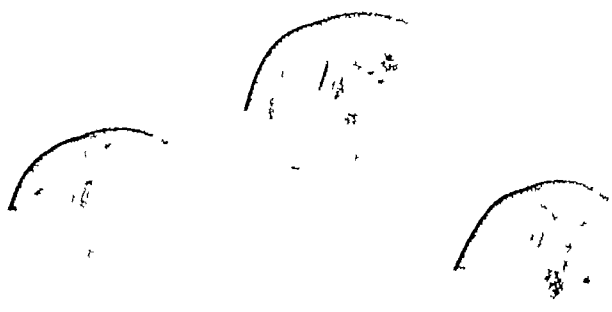
The Executive Offices are busily engaged in preparing the 1928 Supplement to the 1927-28 Year Book of The College. It will be remembered that the Board of Regents determined upon the policy of printing a Year Book only every second year and to print a Supplement, during the intervening years, of the new elections to membership. The 1928 Supplement went to press July 1 and will be distributed about September 1.

## 1928 MEMBERSHIP DUES

The Executive Offices report that there are a number of members who have delayed payment of the 1928 dues and that, in consequence, their names cannot be entered on the subscription list to receive Volume II of Annals of Internal Medicine. It is hoped that all such delinquent members will promptly attend to the payment of their dues. Members delinquent in dues two years may be automatically dropped from the roll of The College.



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# Individualization in Clinical Medicine\*

By JULIUS BAUFER, M D , *Professor of Internal Medicine at the University of Vienna (Austria)*

**M**R President, ladies and gentlemen Before entering upon the subject of my convocation address I feel indebted to give you the assurance of my deep and respectful appreciation It is a great honour not only to myself, but also to our old medical school of Vienna that one of its younger members was selected this year by the Board of Regents of the American College of Physicians to be its guest at the Annual Meeting and to deliver the Convocation Address Concerning the subject of this address I thought it would meet with your approval not to talk about a too specialized and limited subject but to consider a problem of a more or less general medical interest At the same time I thought you might expect to hear something connected with the research work I have been doing myself in the last fifteen years, that is with the physiology and pathology of the human constitution

Among the medical profession and in the scientific discussion of general medical problems we have observed in Central Europe, during the last few years, something like a crisis In medical journals and in medical societies the logical and philosophical basis of the

medical profession is discussed, one likes to establish a sharp line of demarcation between the science of medicine itself and the doctor's medical art which is somewhat more than the pure practical application of a science It is true, the new advances of our knowledge about the vital mechanisms in our organism in health as well as in diseases are remarkable We have at our disposal almost innumerable physical, chemical, serological, biological methods and functional tests by which to elucidate a "case", and to construct a clinical diagnosis from all the symptoms and laboratory findings But the more numerous these methods are, the more difficult is the thorough evaluation of their results, the more frequently a discrepancy between them will be met with There is not always a parallelism between the number of routine-examinations performed in the laboratory of a clinic and the reliability and correctness of the clinical diagnoses on one hand, and the therapeutic results obtained by this clinic on the other hand The reason for this is only in a small degree their insufficiency, and therefore the low value of a great number of all these methods and tests, but to a much greater degree it is due to the fact that a true diagnosis and a suit-

\*Convocation Address, New Orleans meeting, March 9, 1928

able treatment must be based, not only upon methods of a purely collective, or statistical value, but also upon the individual features of a case, upon the personal constitutional characteristics of an individual. The detection of these individual features, the most complete understanding of an individual patient's morbid condition, requires more than the pure evaluation of all possible routine-examinations, it requires a thorough knowledge of the patient's premorbid personality, of its constitutional characteristics including the psychical side which can not be separated from the somatic side of the organism.

A case under my own observation will illustrate better than many words what all this means and how such an individualization in the analysis of a patient's condition is to be understood and executed. I have under my care a surgeon's wife of about 36 who has suffered from gall-stones for many years. Typical colics, a marked tenderness after the attacks, and lately a positive cholecystography permitted this diagnosis with the high probability of nearly 100 per cent. The attacks were released as usually in this disease by a so-called dietetic error, particularly fat food and by psychical emotions. They came particularly at the premenstrual or menstrual period. So far the routine-diagnosis was easily established and as the usual internal routine-treatment did not bring any relief the operation was taken into consideration by the husband. But even if the mortality of an operation were not greater than 1 per cent—in gall-stone operations it is certainly higher—we have to remember the "*primus*

*non nocere*" and we have to consider the possible consequences of a surgical treatment. Let us see what the individual analysis of the case revealed and what good resulted. The first important fact was here that there never were symptoms of an inflammatory process of a cholecystitis, and never symptoms of an obstruction of the bile duct. The subjective symptoms of the disease were only colics due to the spasm of the smooth muscles in the biliary tract. These spasms were released by the quite adequate stimulus of the foreign bodies in the gall bladder. But why did these calculi work as a reflex stimulus only at certain periods at certain intervals? Why can another individual have in his gall-bladder a great number of concretions for years and decades without having a notion of this pathological condition? It was the famous German surgeon Riedel who considered that approximately 95 per cent of all carriers of gall-stones never suffer from that condition. Only 5 per cent would be really ill on account of colic or inflammatory complications. The spasm of the biliary system is released by the concretions—it is true—but only in certain individuals and in our patient only at certain periods, obviously only when the threshold of the nervous irritability was particularly low. Our patient had without any doubt generally a low threshold for nervous stimuli, she was a very sensitive, irritable, nervous person with hereditary marks of a biological—not social—inferiority of the central nervous system. She, and the whole family were of unusual intelligence, but one brother died of a brain tumor, another is a psychopathic

degenerate. The patient as well as her father and her daughter react with delirium to occasional febrile diseases. She had gray hair at the age of 25. Psychological emotions diminish the nervous threshold just as the menstruation does and both are the factors that release the attacks. Concerning the third factor, the dietetic errors, it was easy to establish that the psychic factor rather than the alimentary was the active moment. The fear of getting a colic after a forbidden food was proved experimentally in our case to release attacks whilst the formerly forbidden dish itself had lost this influence after informing the patient as to the neuro-psychical mechanism of the colics. She was fond of mayonnaise, for instance, and ate it sometimes at a social party in spite of it being forbidden by her physician. A gall-bladder colic in the following night was the regular consequence. But the patient could tolerate without the slightest trouble a mayonnaise after she was informed that not the mayonnaise itself, but the consciousness of having eaten something harmful and the fear of an attack was the cause of the colic. It is obvious that the schematic, not individualized, dietetic routine-treatment had harmed our patient more than it had helped her. The simple explanation of the situation and the calming influence of my talk was sufficient to suppress any disorders due to the gall-stones for 8 months. At this time a new colic came immediately after hearing a gentleman's minute description of his own gall-bladder operation which he gave to his neighbour at a social party. I must beg your pardon to have related a simple case

of gall-stones so much in detail, but it is representative of many hundreds of similar and analogous cases not only of gall-bladder trouble but of other conditions as well. It shows that the usual diagnostic label gained by the routine-examinations and put on a case is not quite sufficient, and that we have to proceed beyond the diagnosis of a disease to a thorough analysis of the individual patient in order to complete our conception of what happens in the patient's organism, and in order to raise our therapeutic effects to the highest possible level.

Something of prime importance is illustrated by our patient. She *had* gall-stones and *suffered* from a nervous condition closely related to this organic abnormality. There was not a bit of what we may call hysteria or neurasthenia. Nobody will call this condition a neurosis in spite of the undoubted effects of psychical treatment. It is just a simple case of gall-stones, but it exemplifies that we are quite wrong to separate sharply organic and functional, nervous and psychogenic disorders, that we are wrong to neglect the little psychotherapy of many organic diseases and to say either internist or psychotherapist. Always "*et-et*," always somatic *and* psychic treatment at the same time and in the appropriate dosage and relationship. It is *individualization* in the diagnostic analysis beyond the diagnosis of the disease, and it is *individualization* in the treatment that we want.

In the last few years we have learned by clinical and psychological studies that somatic and psychic processes are so closely connected with each other that we have to deal with a psycho-

physical unity Almost every morbid condition is to a certain extent a psychophysical problem and its elucidation requires a detailed individual somatic and psychic examination, reaching farther than the statement of a usual clinical diagnosis of a disease The clinician must have in his mind every moment, more than is usually done, the important laws of physiology concerning the facilitation of reflexes and particularly the so-called conditional reflexes A reflex mechanism, as coughing or vomiting, may appear during an organic disease as a rather suitable and useful help for the organism It is mobilized by the ill organism as a sort of adaptation in order to facilitate the vital conditions during this disease and to favor the reparation But each time, when this reflex mechanism is activated, the threshold for the afferent nervous stimulus of this reflex is lowered The more frequently the reflex is used the easier it may be released the next time and finally the releasing stimulus becomes not an adequate one any more, the reflex is released periodically by an accumulation of quite physiological stimuli; that means it becomes automatic, spontaneous and has lost entirely its original significance. It is easy to understand that such an automatization of reflex mechanisms is particularly to be seen in primarily nervous and irritable persons and that it is favoured by physiological moments, as hypochondriac anxiety or other related ideas How frequently do we observe such prolonged automatized nervous cough in children after a whooping-cough, in adult after a simple catarrhal affection of the trachea or the bronchi, how

frequently do we see vomiting patients who got accustomed to this prepared reflex by an acute dyspeptic trouble or even by a chronic peptic ulcer, by gall-stones or another organic abdominal condition The hyperemesis gravidarum, the dysmenorrhoeic cramps and many other pathological conditions are to be understood only on the basis of the physiological law of facilitation of reflexes by their own activation

Of an even higher importance for the clinical medicine are the so-called conditional reflexes We owe to Pavlov the exact knowledge of the typical mechanism If an event happens to coincide frequently with the activation of a reflex, then this event itself may acquire the power of the originally releasing stimulus All that needs no further explanation before this forum I remind you only of a well-known experience concerning a case of an anaphylactic bronchial asthma with a hypersensitiveness towards the odor of roses The patient got an asthmatic attack when he was shown an artificial rose of paper The optic impression of a rose so frequently coincided with the releasing action of the antigen that it gained the power to act as a releasing factor itself without the original antigen It is obvious that this mechanism of conditional reflexes plays an important rôle not only in cases of asthma, but also in other pathological processes and that only a careful investigation of the individual can reveal the real situation I had under my care a famous actress who complained of vomiting before playing a certain part I could easily detect the mechanism of a conditional reflex My patient had played just this special part with

great success abroad when she became surprised by a pregnancy with the physiological vomiting. The pregnancy was interrupted but the whole adventure was so effectively accentuated that the playing of this special part became charged with the power of a releasing factor of vomiting.

We internists must not overlook how far the influence of mental processes upon the body may go. Experiences of the last few years illustrate this fact sufficiently. Particularly do hypnosis experiments show that many somatic functions and important physiological acts may be influenced and regulated more by an individual's subjective visional world constructed with the help of a hypnotic suggestion, than by the real environment and by the usual real adequate factors. So it is possible to produce just the same changes in the blood following physiologically the intake of a greater amount of liquid by the pure hypnotic suggestion of drinking (Marx, Schilder and *myself*), we could find the same involuntary reactions, the typical pass-pointing of the hands, if we gave the hypnotic suggestion of being rotated, as after a real rotation of the body. Even the glycosuria and the blood sugar can be diminished by the pure suggestion of an insulin-injection during a deep hypnosis (Gigon). The most interesting experiment of this sort has been related by Hansen and Gessler of Krehl's clinic in Heidelberg. It is old knowledge, that a cooled organism wants more oxygen in order to adapt itself to the lower temperature by increased burning. So it was established that at a temperature of  $59^{\circ}\text{F}$  the basal metabolism was increased about

18%, at a temperature of  $54^{\circ}\text{F}$  about 30%. But cooled persons failed to raise their oxygen consumption as soon as they got the hypnotic suggestion of being in a warm room. On the other hand the basal metabolism rose markedly if the hypnotized person sitting in a heated room was given the suggestion of feeling chilly or of lying undressed in the snow. These experiments seem to be of a far-reaching importance. They demonstrate as clearly as possible that even quite involuntary and unconscious adaptative processes as metabolic functions get rid of the influence of physiological regulatory mechanisms as soon as these mechanisms are not in accordance with the subjective, imaginary situation. The visionary situation governs, the real environment may succumb if it is in contrast to the suggested fiction. The somatic machinery is regulated more by inside-influences than by outside factors if the normal conformity between the subjective and the objective situation is disturbed. Although we have not to deal in practice with complete analogies of the hypnosis experiments, except perhaps certain psychoses, we must always take into consideration the immense influence that psychical factors have upon somatic functions, so that even some of the usual laboratory findings may be modified by emotions, feelings and ideas which are not always recognized and registered by the physician. In addition we must remember how far the psychic side of a patient is influenced by the somatic. The humor, the frame of mind, the mental tonus, is dependent to a high degree on the body and so there may result more fre-

quently than one expects a vicious circle of a psycho-somatic disturbance which has to be understood and considered by the experienced physician

We were taught to recognize disturbances of the human machinery and how to improve or to repair them. And this is quite right. But we must not forget, that it is not always an organic disturbance of the machinery itself that brings the patient to the doctor. Frequently he comes on account of unpleasant sensations, due to his organic disturbance only to a certain extent, and in part due to the patient's inclination for such a sort of feeling. What one person does not even notice may bother another extremely, particularly if a psychical repercussion is associated with the sensations. He who intends only to influence and to repair the disturbed machinery and does not care for this individual point of psychical repercussion is not a far-seeing physician, at least he does not make use of all opportunities of therapeutical results. It may be that in such a case a quack helps the patient better than the doctor, although he does not care at all for the defect of the machinery because he can not even understand it. It is harsh and disagreeable, indeed, to say these words before the profession, but first the truth must be recognized and accepted in order to fight against the error. Some examples may illustrate this situation.

Not infrequently we see in our office patients affected with a well compensated heart lesion complaining of palpitation and unpleasant ill-defined heart sensations. These sensations are often due to the increased atten-

tion paid to the heart by the patient on account of his knowledge of the valvular defect. The affective participation is quite a natural consequence and any treatment directed towards the fully compensated lesion is not only superfluous but even harmful because of its bad influence upon such a patient's mental attitude. A simple explanation and calming of these persons will help them. How frequently do we meet with enteroptotic asthenic nervous women whose troubles are not due to the ptosis of their kidney, colon or stomach, or to the retroflexion of their uterus, but are due to the consciousness of something wrong, something ptotic or displaced in their abdomen. This information given them by a physician increased, or even initiated, their unpleasant sensations. Therefore it is of the greatest importance to know that such a ptosis of the stomach, colon, kidneys and so on may be a constitutional characteristic of many thin, frequently asthenic, and almost regularly nervous persons. The same ptosis may be found during the whole life but the subjective troubles are only temporary and quite independent of the degree of the ptosis. The diagnostic label "enteroptosis" is frequently erroneous because it indicates only a constitutional type and does not touch the real mechanism of the complaints.

Quite a separate chapter are the hypertension patients. It is by no means exceptional to reveal a marked arterial hypertension as a purely accidental finding in persons who are examined thoroughly without showing any subjective symptoms of their vascular condition. For the patient it

may be quite a critical moment of his life to hear now about his arterial hypertension and to get prescriptions and advices concerning his future life. If he had felt perfectly all-right up to the moment of this consultation, he may become a broken man after that time and may live as a *wreck* the rest of his life, interested chiefly or exclusively in his blood pressure. Besides that this increased blood pressure may not even show a tendency to react to the different treatments. We must conclude that the routine-treatment directed against the disturbed machinery solely, that is against the hypotension, did not only fail entirely but was the cause of serious subjective disorders. We have to take into consideration and to check up before any information and treatment of a patient, the seriousness of the disturbance of his machinery, the probably repercussion on his psyche and the value of our prescriptions and advice.

Perhaps we are too circumstantial in discussing the highly important psychical side of the problem of medical individualization, and if we turn our attention to other questions related to this problem, we may use the example of hypertension first in order to illustrate a principal point. Why do we meet with an entirely different symptomatology in different cases of hypertension? The same anatomical and functional condition, the same degree of arterial hypertension may produce shortness of breath or aortalgia in one person, headache or dizziness in another, rheumatic pain in a third and may not bother at all a fourth. It may kill one patient by an apoplectic stroke, another by an insufficiency of

the hypertrophied left ventricle with the subsequent lung edema and a third by a renal insufficiency and the subsequent uremia. The individually different progression of the anatomical changes in the small arteries, the individually different involvement of special parts of the peripheral blood vessels, the individually different reactivity and resistance of the heart muscle and the varying tendency of the overdistended arteries to spastic contractions in different parts of the body are to be considered as the chief causes of the variability of the clinical picture of the genuine permanent arterial hypertension. The physician who watches carefully the family history of his patients will be convinced that constitutional factors are here of undoubted influence. Sometimes we may meet with particularly interesting mechanisms explaining the special symptomatology of an individual case. I was consulted once by a gentleman of 54 on account of a constant slight dizziness which was certainly to be attributed to a moderate hypertension of 180. No other symptoms were to be found except a partial deafness of the right ear. The man had suffered since his 18th year from typical fits of Ménière in rather long intervals due to the lesion of his ear. His mother and sister suffered from migraine. It seems probable that the involvement of the static apparatus in the widest sense by the Ménière's disease was the determining factor of the special symptomatology of the beginning hypertension. The old Ménière facilitated the sensation of dizziness now provoked by the arterial hypertension. It was a sort of facilitation which prepared



this particular clinical picture of hypertension

Everyone is familiar with the rather various clinical forms of heart decompensation. A great many of these individual differences are due to the different involvement of the right or left part of the heart and are easily explained by purely mechanical factors. It was particularly Wenckebach of Vienna who pointed out, how the prevailing congestion of the lungs or of the liver included the portal circulation, how in other cases the predominant congestion in the cava superior may be explained by mechanical factors only. In spite of this statement we have to acknowledge the observation of Kretz, Jr., of Vienna concerning the different reaction of thin, asthenic people and broad-shaped, rather well nourished, pyknic individuals upon a heart decompensation. The first group, the longitudinal type, has generally a greater tendency to congested and prominent veins, to cyanosis, to liver- and lung-congestion, to embolism and hemorrhage, but is not inclined to edema, the second, the broad, lateral type, shows the very opposite reaction, the tendency to edema and to dropsy of the great body cavities. There is no doubt about the individually different tendency of the tissues to develop edema. The avidity for water is certainly greater in a skin containing a considerable layer of subcutaneous fat. We meet with this coincidence of fat and of water avidity of mesenchyma also in a quite different pathological condition, that is in certain cases of lipomatosis. I saw recently a case of otherwise well compensated mitral insufficiency with a very obstinate slight

edema of the legs, disappearing after a night's rest but being present in upright position for many years in spite of all treatments and a rather sufficient digitalization. The patient, a lady of about 45, had at the same time a moderate and localized lipomatosis of the legs which was even more striking in her sister and niece. This constitutional characteristic determined the extreme disposition to the development of cardiac edema.

One of the most interesting examples pointing towards the necessity of individualization is the condition called hemolytic anemia or hemolytic jaundice. Usually one separates two types of this disease, a congenital and an acquired. That is wrong in my opinion. Even the apparently acquired cases are, according to my own observations, constitutional, although latent up to the moment of the action of a releasing factor, as pregnancy, syphilitic infection and so on. They were latent by compensation and became manifest by an insufficiency of the over-strained compensating organs. In the families of those patients we may find by chance individuals who feel perfectly healthy but show definite signs of their constitutional abnormality. One of these practically healthy family-members may show a markedly decreased osmotic resistance of his red blood corpuscles with or without an enlarged spleen, another may show a considerable hyperbilirubinemia and urobilinuria, a third an aniso- and microcytosis of his blood. All these individuals need not have any anemia or jaundice as long as the bone marrow and the liver are sufficiently compensating the precipitate

blood moulting. But they have to work harder in such a person whose erythrocytes live a shorter time than normals because of their premature destruction in the spleen and liver.

All our organs work at a certain optimum and possess a reserve power of an individually different degree. If they are overstrained to the maximum of their reserve power then the insufficiency, and consequently the functional disturbances of the machinery, are inevitable. In this instance it is the biological value and the adaptative power of the bone marrow on one side and of the liver on the other side which decide whether such an "hyperhemolytic" individual, if I may use this term, lives healthy without disorders or whether he develops a hemolytic anemia or a hemolytic jaundice. What we may find in such a compensated case, the enlargement of the liver or of the spleen, the low osmotic resistance of the red blood corpuscles, the hyperbilirubinemia or urobilinuria are not yet symptoms of a disease but are indicators of a constitutional deviation bearing upon the physiological "moulting" of the red blood cells. These individuals are not ill, but they are highly disposed to develop the illness at a most trivial occasion or spontaneously by an exhaustion of the overstrained organs.

To discuss the problem of individualization in cases of tuberculosis is almost impossible, but it seems rather superfluous as every experienced physician knows about the striking individual differences in the clinical picture, in the outcome and the effects of the applied treatment. These differences are not only due to the infec-

tion with different strains of bacilli or to their different quantity and virulence, but they are also to be attributed to the various culture media presented by various individuals. I had a patient suffering from a lupus vulgaris and affected with a pathological obesity. The tuberculous infection came without any doubt from the father who was suffering, as well as his brother and sister, from a chest tuberculosis. These three persons were thin and had a longitudinal, asthenic habitus. The father infected two of his children, but no one developed a pulmonary condition, one had a lupus, the other lymphomata colli. All children had inherited the mother's habitus and were, just as the whole mother's family, extremely stout. A body weight of 200-300 lb was the rule among these people. May one deny that the Koch bacilli growing in the father's lung grew differently in the entirely different culture medium of the obese race? They did not affect the chest but other organs of this race. Can it be a pure accident, if the American urologist Kretschmer describes a renal tuberculosis in identical twins, girls 14 years of age? Only the identical bacterial culture medium of the identical constitution can explain satisfactorily this striking coincidence of a not at all frequent condition.

The most important rôle played by the individual constitution is in endocrine disorders. Many of the frequently alleged endocrine symptoms are to be attributed to a primary constitutional anomaly of this very individual and have nothing to do with the endocrine glands, or at least they are not due wholly to endocrine disorders.

I had the honor to point out more in detail some of these highly interesting questions 4 years ago in this country, and my address has been published in the American Journal of Endocrinology of 1924. It would go too far to discuss that to-day anew and I will confine myself to drawing your attention only to the most different symptomatology of one and the same endocrine disturbance in different individuals. It needs no further discussion that the same degree and sort of thyroid insufficiency may produce in one man a marked psychical sluggishness and nervous disturbance, in another a marked anemia or the typical skin changes, in a third an obstinate constipation, or serious so-called rheumatic pain, in a fourth heart trouble or a progressive obesity. In the moderate, oligosymptomatic cases the arrangement of hypothyroid symptoms is individually different. If the lack of thyroxin is a complete, or nearly complete one, then each part of the organism will show the typical features of the insufficient supply of the hormone. If the lack of thyroxin is only partial then the consequences of the insufficient hormonization will become manifest in a various degree in different organs. Some organs will show their insufficient hormonal regulation earlier and more than others. That depends on the individually different constellation of the biological value of the organs, whether an organ or a special function requires more, or less, of the hormonal stimulus or whether it is secured by its own autochthonous mechanism. I spoke of a "principle of multiple safety" governing the function of our organs. They are secured by

their own structure and "Anlage", but they are secured also by a hormonal and by a nervous regulation. The various degrees of each of these three safety mechanisms explain the various clinical picture in oligosymptomatic, that is partial, endocrine disorders.

What is true for the thyroid insufficiency is true also for the hyperthyroid conditions. The leading symptoms of these oligosymptomatic cases may vary considerably. At one time it is tachycardia and palpitation, at other times tremor and nervousness, even psychical disturbances, or serious vasomotor symptoms, at other times diarrheas, and dyspeptic disorders, or it may be a rapid loss in weight, or a glycosuria which induces the individual to consult a physician. Quite a different clinical picture, but an identical causal factor, one and the same hyperthyroidism! The different individual reactivity of the peripheral organs upon the exaggerated hormone-supply is due to their different biological value and the safety mechanism of their function. We can observe regularly that individuals with predominant heart symptoms in a hyperthyroidism originate from a sort of heart-family where other members suffer from other heart conditions, we see patients with hyperthyroid diarrhea originating from gastro-intestinal families and so on. In any event, the clinical picture of all these incomplete endocrine disorders is never dependent upon the glandular lesion alone but always also upon the individual constitution with the consequently various hormonal reactivity of the organs.

We meet in practice with all borderline cases from the complete defi-

ciency, or the most extreme abundance of the hormone to the normal condition, from the classical clinical pictures through the rudimentary, oligosymptomatic cases to the normal. In this way we may see once in a while a case which we may designate as monosymptomatic, as, for instance, a simple tachycardia or a constipation which is considered as a monosymptomatic form of hyper- or hypothyroidism. But this assumption does not seem logical. In a pure monosymptomatic endocrine case where only one single symptom would betray the endocrine anomaly, it is practically not the endocrine function which is altered, but it is reactivity of one single organ upon the hormone, because the amount and quality of this hormone is obviously appropriate for the requirement of all other organs and is apparently insufficient or exaggerated only for the single organ giving rise to the term monosymptomatic endocrine disorder. We see, therefore, that monosymptomatic endocrine disorders are not to be acknowledged, they do not exist actually, and we meet with the greatest difficulties of classifying some special clinical cases according to the rôle played by the endocrines, by the vegetative nervous system and by the organs themselves in the production of pathological symptoms. Only a thorough examination and individual analysis of the case, with reference also to the family history, will help us to understand the pathological mechanism and will prevent us from the most disgusting abuse of the endocrine glands in a pseudo-explanation which seems to be satisfactory but is only modern. Individualization is indispensable also in this field of clinical medicine and we must

take into consideration the psychical side of a patient just as at any other time.

I am afraid that my talk has tired you since you have heard nothing new but only old and well-known facts, at least known to you through your own practical experience, if not through your medical studies. It is true, there is a difference between the pure medical science and the art of its practical application at the patient's bedside. This art is somewhat more, indeed, than this application only, it requires more than a complete knowledge of all scientific details, it is and will be always an art which never will be transformed into an exact science, as the complete understanding of one person's psychophysical machinery never will permit us to understand a second man's personality just as well by a pure analogy, because of the practically infinite variability of the individual constitution. The individual analysis must start always anew, and what science of the human constitution may help, is only to establish certain groups of more or less pronounced common characteristics in somatic structure, in physiological and pathological functions, in the reactivity to exogenous and endogenous stimuli and disorders, but it will never replace entirely the doctor's art to reveal the individual particularities of his patient and to take them into consideration in analyzing the pathogenesis of a patient, in constructing his diagnosis and in applying the fitted treatment. The medical science must be and will remain always the indispensable solid basis of a doctor's art, but this medical art must be the aim of the profession and the aim of medical education.

# A Review of Research in Yellow Fever\*

By ARISTIDES AGRAMONTI, M D, *University of Havana, Cuba*

WHEN we contemplate, in our present security from yellow fever, all that has been suffered by other communities, none less than this one of your beautiful city, in the terrible days now fortunately past, but which extended even to our present generation, when we realize the incalculable number of lives that have been preserved through the conquest of that scourge, when we look about us and observe the material progress that has been attained by the apparently simple fact that we can prevent the occurrence of epidemics, when we visit the Panama Canal and remember that it was made possible only through a proper sanitary control during its construction, and how Vera Cruz, Havana, Rio de Janeiro, Guayaquil and other cities have become, not only perfectly habitable by the white man, but in some instances, as in the case of my own city, (Havana,) they well deserve now to be considered as health resorts, when we realize all these things, we cannot help but become appreciative of the value of the work which those who have gone before us undertook and carried out so successfully

The origin of this malady has been the subject of much learned discussion and deserves that we consider it, if only very briefly, inasmuch as the most active and effective investigations have been undertaken in America

If we leave out of consideration the equivocal Maya writings and the exaggerated and often visionary histories provided by the Spanish adventurers and colonizers of the XV Century, as I am inclined to do, if we compare the period at which the indisputable epidemics of yellow fever did appear in this hemisphere with other contemporary circumstances, we cannot but remark that only after the introduction of the black slave trade, did yellow fever become evident amongst any white population. Investigation carried out in our present century, has shown that it was not unknown along the West coast of Africa, we can hardly presume for how long, until it was clearly pointed out by Robert Boyce, of the Liverpool School of Tropical Medicine, in 1910, since then, several perfectly well-defined epidemics have been described and a focus of endemic yellow fever has been demonstrated there, it is evident that the disease is maintained among the blacks endemically, exploding in epidemic form at irregular periods among the comparatively few white inhabi-

\*Read before the American College of Physicians, Annual Clinical Week, March 9, 1928, New Orleans, La

ants, making thus an immune element from those who survive and repeating the process when there is a new influx of non-immune residents in the towns. The isolated condition of that part of the world, with relation to the countries inhabited by a white population and the total absence of emigration from West Africa to European or other states, has probably been the reason why our attention had not been directed to those parts as a possible source of yellow fever, until the last twenty years.

From the time that it became implanted in the West Indies, as an importation, be it from the mainland or from Africa, it remained there for fully two and a half centuries, serving as a constant menace to other territories in America and in Europe. The cities of Havana, Vera Cruz, Panama, Guayaquil and Rio de Janeiro became well-known plague spots and were shunned by travel and trade, as much as possible, during the summer months. From them and from the Lesser Antilles which were practically neglected from a sanitary standpoint, the disease traveled North and South, only seventeen years after the settlement of Philadelphia, (1699,) it was visited by a yellow fever epidemic, more dreadfully in subsequent years, (1741, 1747, 1762,) each time certainly imported from the South, (Charleston and other towns that had been invaded from the Caribbean Islands,) but in the year 1793 the appearance of the disease was accompanied by such a mortality that it carried panic into the homes and caused a great exodus from the city, in the short space of a month and a half, more than 4,000 deaths occurred

in a population of 40,000 people. The first half of the XIX Century was particularly rife in yellow fever epidemics, extending over the widest territory that it has been known to cover till then and since then, it spread from America to southern Spain, to some ports of France, to Leghorn, Italy, and the southern United States. While in all these places the epidemics were regularly terminated with the advent of autumn and winter, the disease smouldered uninterruptedly in the Caribbean and Gulf coasts of America throughout the year. The sanitary history of your own city during the last century is a salient example of what woe and misery always attended the invasion of a non-immune community by this disease.

The number of lives sacrificed to our ignorance of its epidemiology and etiology, certainly reaches to many hundred thousands, there are not very clear records from the French and Spanish possessions, but those of cities along the Atlantic coast and the Mississippi valley show that the figures above quoted are not exaggerated. The amount of money it has cost through loss of life, interruption of business and trade and unnecessary expense, if it could be calculated, would be found to be many millions of dollars.

In truth, my subject does not deal directly with these matters, but it is important that we keep them in mind, better to appreciate the blessing of immunity we now enjoy and the happy future that we dare to foresee and foretell.

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Naturally, during the earliest period in the history of yellow fever, the most

prominent physicians of the time, particularly of the regions affected, became intensely interested in its investigation; however, this was necessarily limited to a study of the symptomatology, a comparison with alleged similar conditions or diseases and the consideration of numerous hypothetical questions as to its sources and methods of transmission. A glance over the literature, which is astonishingly vast, reveals wonderful sagacity, power of observation and deduction on the part of many practitioners not otherwise renowned. The names of DuTertre, Rush, Caldwell, Massie, Chervin, LaRoche and many others forming legion, appear in exhaustive papers and monographs pertaining to the study of this disease, their activities were restricted to personal observation of cases, detective functions tending to discover the hidden method of their dissemination, depending greatly on hearsay information from very unreliable sources, resulting in their work, on the main, in a series of generally erroneous presumptions and theories. Important factors in misleading the most painstaking and earnest investigators were, undoubtedly, the belief in spontaneous generation, in the action of mephitic air or miasms, in the noxious influence upon the atmosphere of accumulated excreta, in the action of poisonous gases evolved from the bilge water of ships, to say nothing of the influence superstitiously attributed to the heavenly bodies.

Until the later part of the XIX Century, investigators were deprived of the aid of laboratory or experimental facilities. In fact, it was with the birth and development of bacteriology that

the first attempts at a really scientific research were made.

For the purpose of this address, I have divided the subject matter into two periods; the first, embracing the last quarter of the last century, and the second, from the year 1900 to the present date, taking in review the principal attempts and failures and the reasons for them, and the successful efforts of the more recent investigators.

Alas! the failures far surpass the successes, but each in its own way carries a lesson that we might profit by, and if as yet we have not been enabled to grasp the elusive parasite, that seems not to be of paramount importance if our aims tend, as they should, by all means to the extirpation of yellow fever from the earth, and I feel that we should be much elated at the present outlook, the disease having virtually been driven to its last redoubt, upon the western coast of the Dark Continent.

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#### THE PERIOD PREVIOUS TO 1900

It is rather unfortunate that some of the men who have worked in an attempt to elucidate the problems connected with yellow fever, its etiology and propagation, were not always inspired primarily by the desire to discover the truth and thus contribute to the welfare of humanity; when we closely scrutinize the claims and the announcements of these men, we are sorry to find that even some few who enjoyed high prestige among their fellow citizens, upon more than one occasion, directed their labors and their results to their own benefit. In this respect, the work of the last century

was very unlike that carried out during the present one in which the investigators expected no material reward for their labors, having performed them in the line of duty, and the millions that have been spent from public as well as private funds were used so exclusively in carrying out laboratory and experimental research and such general sanitation as will probably cause in due time the total extinction of yellow fever.

From the year 1880 to 1887, Dr Domingos Freire, in Rio de Janeiro, Brazil, was engaged in applying what might have been considered then as modern bacteriologic methods in his investigation of yellow fever and finally claimed to have found the cause of the disease in an organism presumably isolated from the blood and tissues of such cases which organism, after due (and probably secret) manipulation could be employed to immunize susceptible individuals. The statistics presented to back up such assertions were very encouraging.

From a careful study of the methods employed and the trend of Dr Freire's investigations, it is evident that he had in mind, to the exclusion of every other thought, the finding of some micro-organism that would answer to what he believed were the requirements of the yellow fever germ. He had limited his investigations to obtaining cultures, but no further study was made of them, nor of the tissues from which they were at times obtained. The tubes containing them he even took to Europe in an effort to secure scientific sanction from the bacteriologists of that time. The organism, supposed to have been uniformly

isolated from cases and cadavers of yellow fever, upon investigation proved to be the common staphylococcus albus, it in no way corresponded to the descriptions made of the *Cryptococcus xanthogenicus*. But the worst aspect of all the story connected with this scientific swindle rested upon the fact that by means of a supposedly attenuated strain, vaccinations with this organism were practiced in a large scale upon the non-immune population. The Brazilian Government went to the extent of appropriating funds for the preparation and application of the yellow fever vaccine, learned and scientific bodies heaped honors upon the instigator of this fraud, while people continued to contract the disease and the same proportion as before the inoculations, died of it.

Major Geo M Sternberg, U S Army, having been detailed for the purpose, after careful investigation says

"Having reviewed at length the claim of Dr Domingos Freire to have discovered the specific germ of yellow fever and to have transmitted this disease to certain lower animals by inoculation, and having arrived at the conclusion that these claims are without scientific foundation, it may be thought that no further demonstration is required in order to show that his protective inoculations are without value. The inoculations practiced are said to be made with cultures containing the attenuated microbe of yellow fever, *a priori* it would appear that if there has been no veritable discovery, and if there is no sufficient evidence that the cultures used contained the



specific germ of yellow fever, no value can be attached to such inoculations "

This practically put an end to Freire's claim, but with the notoriety obtained and the aid of influential friends in the government of his country, the preventive inoculations continued for some time and the inventor waxed rich and prominent

At the same time that the Freire hoax was being perpetrated in Brazil, (1885-1887,) another investigator, in Mexico, was putting forth a similar claim, affirming that he had discovered a definite and specific organism in the blood and urine of yellow fever cases. It is curious, in connection with this work, that Dr Carmona y Valle never obtained the material himself, but had it brought to him from quite a distance, by his associates

The cultures which he presented to Dr Sternberg, who having finished with the Freire investigation went after this Mexican claim, contained both a micrococcus and a bacillus. When asked about this peculiar symbiosis, Dr Carmona explained that his idea was that the micrococci were "zoospores" which subsequently germinated in the form of bacilli and that the latter, in time, broke up into spherical bodies. The persistence of brownian movement in the so-called "zoospores" was to him sure proof of their great vitality and resistance to destructive agencies. These fallacious results could not withstand the careful scrutiny to which they were subjected and their worthlessness was soon demonstrated

Dr Carlos J Finlay, of Havana, in 1881, as we shall see later, announced his theory that yellow fever was trans-

mitted from man to man by the bites of mosquitoes. Imbued with the spirit of bacteriological research that dominated at the time, with reference to infectious diseases, he undertook, with the assistance of Dr Claudio Delgado, who had acquired some laboratory training abroad, to obtain cultures of such organisms as might be accused, more or less justly, of being the yellow fever parasite. In the years 1886-1887, these investigators gave as a result of their work a tetracoccus, (*micrococcus tetragenus versatilis*, Sternberg,) and probably other tetracocci in plantings made from finger blood, blister serum and secretions, (tears, urine, etc.) of yellow fever patients

Inasmuch as five years before, Dr Finlay had indicated that mosquitoes were the disseminators of the yellow fever germ, it became urgent to show that these insects took into their tissues the organism, later supposed to be the cause of the disease. With this object in view, and believing erroneously as we know now, that the mosquito was in condition to transmit the infection as soon as it bit again, after becoming gorged with yellow fever blood, it was logical to suppose that the causative germ should be found in its proboscis immediately after feeding. In the numerous experiments carried out, not only the mosquito's sting and head were planted in various media, but it is described how some of the insects were seen to peck at the agar media and by the introduction of their proboscis, caused the subsequent development of tetracoccus colonies

It is reported that only the particular tetracoccus resulted from these experiments and the natural deduction was

that, not only the means of transmission, but also the etiologic agent had been demonstrated. Unfortunately, neither the one nor the other could be corroborated at the time. Dr Sternberg's Report, where he dismisses the question of Finlay's bacteria, says "There is no reason to believe that this organism has anything to do with the etiology of yellow fever and its occasional presence in blood drawn from the finger or in blister serum, is due to accidental contamination from the surface of the body or from the atmosphere."

A poignant lesson may be derived, however, from this series of experiments, it shows how even a master mind can go astray, not only when it deviates and plunges through the unexplored byways of new techniques, but specially when it is instigated by desire, unwilling, yet evident, to fit the apparently indisputable facts, to preconceived ideas.

Please notice how men were working with avidity to solve the problem of yellow fever in the very foci of infection and mostly at about the same time, they were trying to take advantage of the methods that had been so successful in discovering the etiologic agents in tuberculosis, leprosy, anthrax, diphtheria, tetanus, typhoid fever, etc.

Probably the first investigator who abandoned the theory that the infection of yellow fever took place in the blood, was Dr Paul Gibier, in Havana, he directed his researches to the alimentary tract. In this way, by employing the most scientific technique up to that time, he isolated a bacillus which was equally demonstrated by

Sternberg to have been of no importance.

With the possible exception of Gibier, thus far, only men with little or no standing as bacteriologists had engaged in the fruitless search for the yellow fever germ, and their claims, as we have seen were quickly disposed of, but in 1897, a well-known investigator, Dr Giovanni Sanarelli, who had obtained some renown by his work in the Pasteur Institute, particularly with typhoid fever, published a remarkable paper in the *Annales* of that institution, which on the most careful examination bore the imprint of truth. This report of the work carried out in Montevideo, Uruguay, was published in several languages, and in a comparatively short time the whole scientific world tacitly accepted Sanarelli's bacillus, (*Bacillus icteroides*), and anxiously awaited the prophylactic serum which he announced as already undergoing manufacture.

Cultures of the *B. icteroides* were secured by various laboratories and experimental work begun for the purpose of verifying his findings, the results were most disappointing for the lack of uniformity.

Sanarelli did not fail to have staunch supporters for a while. De Lacerda and Ramos, in Brazil, though accepting the specificity of *B. icteroides*, endowed it with the most astounding pleomorphism. Dr O. L. Pothier, though having found it only in three, out of fifty, yellow fever autopsies, at the Isolation Hospital in this city, (New Orleans,) concluded that "it is the special cause of yellow fever."

Drs Wasdin and Geddings of the Marine Hospital Service, in a prelimi-

nary and separate report of work performed during the same epidemic, claimed to have found *B. ictteroides* in thirteen out of sixteen cultures made from yellow fever cadavers, (the number not stated,) and Geddings declared that their "results indicate that the *B. ictteroides* of Sanarelli is the specific agent in the causation of yellow fever"

In July, 1899, these gentlemen presented a complete and final report, the gist of which was that "in the blood of yellow fever cases extracted during life, *Bacillus ictteroides* has been found in thirteen of the fourteen cases, with one negative, a percentage of 92.85"

Achinard and Woodson had also a leaning towards *B. ictteroides* and claimed to have isolated it in 80% of cases in New Orleans

More than ten other investigators in Brazil, Uruguay and Italy, by multiple experiments tried to demonstrate the validity of Sanarelli's contention

It happened at the time that I was also engaged, under instructions from Surgeon General Sternberg, in the very same work as Wasdin and Geddings, in Havana. We frequently met at the autopsy table or in the hospital wards, so that the same cases served our purposes. I always made the autopsies and we all secured material and made plantings from the same cases. In due time, I rendered my report, (November, 1899,) including a period of six weeks spent at the yellow fever hospital in Santiago. My conclusions were as follows

1 The specific organism in yellow fever is as yet an unknown entity in spite of the work reported by various observers, apparently new methods of cultivation must be introduced or new

culture media devised in future research

2 The *B. ictteroides* of Sanarelli, lately asserted to be the causative agent of yellow fever is no more concerned in the production of this disease, than the common colon bacilli which are constantly found in the blood and viscera of individuals suffering or dead from yellow fever

3 When approved bacteriologic methods are employed, the bacillus of Sanarelli does not as a rule appear in the cultures from the blood of yellow fever cases

4 *Bacillus ictteroides* may be and has been found present in the tissues of cadavers from other diseases

5 The bacillus of Sanarelli when subjected to agglutination tests is not affected by the serum of yellow fever patients or convalescents

In the meantime, Reed and Carroll, at the Army Medical School, had shown that *B. ictteroides* belonged to the hog-cholera group of bacteria

With all this evidence against it, *B. ictteroides* would have been forgotten, after having entered all the contemporary text-books as the specific agent of yellow fever, had it not been that after the mosquito transmission of the disease had been demonstrated, some work was undertaken in this city, (New Orleans,) with the idea of bringing out whether the bacilli could not be passed around by the insects, through biting various animals

Sanarelli in 1898 very quickly sold out his interest in the coming yellow fever prophylactic serum, in Montevideo, and sailed for home, far from the fields of investigation, he was

then appointed Professor of Hygiene in the University of Bologna, Italy, and subsequently became a Senator. As you know, from the viewpoint of science, he is quite dead.

I have gone a little more deeply into the Sanarelli boom of twenty-nine years ago because I think a lesson can be derived from his activities and the stand taken by most honorable men in his support. It shows how a world-wide reputation, backed by enthusiastic though misguided investigators, can impose upon the scientific world a so-called parasite, to the extent of obtaining general acclaim and acceptance, overriding many apparently reasonable objections requiring much time and painstaking labor on the part of others, before it could be knocked and definitely buried in oblivion.

In the field of yellow fever research, that work of demolition, so necessary at times, is much more difficult today than it was then, mainly for lack of material and the great expense entailed by the need of expeditions to distant lands.

However, as truth is bound to come out, resplendent, in the end, it is sure to do so now, as it did then.

#### PERIOD FROM 1900 TO DATE

From the facts noted heretofore we see, that with regard to the etiology of yellow fever nothing really had been accomplished up to the present century. Much had been done, however, in the study of the clinical and pathological aspects of the disease, the names of J. W. Ross, Stanford Chaillé, John Guitéras, Geo. M. Sternberg, Henry R. Carter and others, shall ever

appear in the history of yellow fever as shining marks in their respective places.

After one year of military occupation of the Island of Cuba and the implantation of many sanitary improvements, it was found that the condition, as far as yellow fever was concerned, had not been materially affected, on the contrary, with the establishment of better and frequent communication with other towns, from Havana, epidemics broke out in new foci, a severe one developed in Santiago, (1899,) while the capital and its suburbs continued to be a source of worry to the sanitary authorities.

In May, 1900, the Surgeon General of the Army appointed a Board of medical officers, consisting of Maj. Walter Reed, as chairman, and Drs. James Carroll, Jesse W. Lazear and myself, officially to investigate the infectious diseases in the Island, but with instructions to devote special attention to the problems of yellow fever.

The Board convened on the 25th of June and learned of the direct and verbal instructions received by Maj. Reed from Gen. Sternberg. The work was distributed, by Reed assuming the direction, Carroll to do the bacteriologic and Lazear the pathological investigations, while I was to perform the autopsies and do the clinical work, having at the time charge of the Division Laboratory and a Ward for Tropical diseases at Military Hospital No. 1, in Havana.

During the month of July the work continued as above outlined in a more or less routine manner. An epidemic of yellow fever developed in

Santa Clara, a city in the center of the Island and eight hours from Havana by rail, several soldiers died from the disease and I was detailed to make such investigation as might trace the source of the epidemic and aid the medical authorities in establishing whatever preventive measures might seem proper. Capt J Hamilton Stone, in charge of the Military Hospital, had already done much of this and so upon this occasion and only incidentally, Capt Stone and I spoke of the possible agency of insects in spreading the disease.

As to the actual cause of yellow fever we were still entirely at sea, it helped us little to know that a man could become infected in Havana, take the train for a town in the interior and start an outbreak there in the course of time.

In the early days of July, reports came from the troops stationed at the town of Pinar del Rio, in the western part of the Island, of a so-called epidemic of "pernicious malarial fever." I received orders to proceed there and report the actual condition of things. Upon the day of my arrival, July 19th, a soldier had just died of the fever, the autopsy revealed to me that he had died of yellow fever, a survey of the sick in camp and an examination of charts and records of previous cases, led me to report the existence of a severe epidemic and to initiate measures of isolation and the removal of the camp into the country. Major Reed joined me two days after and together we went over the records of the camp and hospital. Here we seemed to be in the

presence of the same phenomenon remarked by Capt. Stone in reference to the cases at Santa Clara and before that, by several investigators of yellow fever epidemics, the infection at a distance, the apparently harmless quality of bedding and clothing of the sick. The possibility that some insect might be concerned in spreading the disease deeply impressed us and Maj Reed mentions this circumstance in his later writings.

This was really the first time that the mosquito transmission theory was seriously considered by members of the Board and it was decided that, although discredited in spite of the repeated attempts of its most ardent supporter, Dr Carlos J Finlay, to demonstrate it, the matter should be taken up by the Board and thoroughly sifted.

On the first day of August the Board met and determined to investigate mosquitoes in connection with the spread of yellow fever. As Lazear was the only one of us who had had any experience with mosquito work, Maj Reed thought proper that he should take charge of this part of the investigation in the beginning, while we, (Carroll and I,) continued with the other work at hand, at the same time that we became familiar with the manipulations necessary in dealing with the insects.

A visit was now paid to Dr Finlay who, much elated at the news that the Board was about to investigate his pet theory, the transmission of yellow fever from man to man by mosquitoes, very kindly explained to us many points regarding the life of the one kind he thought most guilty and ended by furnishing us with a number of

eggs which, laid by a female mosquito nearly a month before, had remained unhatched on the inside of a half empty bowl of water in his library

Much to our disappointment and regret, during the first week in August, Maj Reed was recalled to Washington that he might, in collaboration with Drs Vaughn and Shakespeare, complete the report on "Typhoid Fever in the Army." Thus we were deprived of his able counsel during the first part of the mosquito research. Maj Reed was detained longer than he had expected and could not return to Cuba until early in October, several days after Lazear's death.

The mosquito eggs obtained from Dr Finlay hatched out in due time, the insects sent to Dr L. O. Howard, of Washington for their classification were declared to be *Culex fasciatus*, later they have received various names and are now known as *Aedes aegypti*.

Lazear applied some of these mosquitoes to cases of yellow fever at "Las Animas" Hospital, keeping them in separate glass tubes properly labeled and everything connected with their bitings was carefully recorded, the original batch soon died and the work was carried on with subsequent generations from the same.

The lack of material at Quemados, near Havana, caused us to remove our field of action to the city, where cases of yellow fever continued to appear. We met almost every day at "Las Animas" Hospital, where Lazear was trying to infect his mosquitoes, or now and then I performed an autopsy and Carroll secured sufficient cultures to last him for several days of bacteriologic investigation.

Considering that, in case our surmise as to the insects' action should prove to be correct, it was dangerous to introduce infected mosquitoes amongst a population of 1,400 non-immune soldiers at Camp Columbia, Dr Lazear thought best to keep his presumably infected insects in my laboratory at the Military Hospital No 1, from where he carried them back and forth to the patients who were periodically bitten.

Incidentally, after the mosquitoes fed upon the yellow fever patients, they were applied, at intervals of two or three days, to whoever would consent to run the risk of contracting yellow fever in this way, needless to say, current opinion was against this probability and as time passed, and numerous individuals who had been bitten by insects that had previously fed upon yellow fever blood remained unaffected, I must confess that even the members of the Board who at first were rather sanguine in their expectations, became somewhat discouraged and their faith in success very much shaken.

Although the Board had thought proper to run the same risks, if any, as those who willingly and knowingly subjected themselves to the bites of the supposedly infected insects, opportunity did not offer itself readily, since Maj Reed was away in Washington and Carroll, at Camp Columbia, engrossed in his bacteriologic investigations came to Havana only when an autopsy was on hand or a particularly interesting case came up for study. And so time passed and several Americans and Spaniards had subjected themselves in a sporting mood to be

bitten by the infected (?) mosquitoes without their suffering any untoward results, when Lazear applied to himself, (August 16th, 1900,) a mosquito which ten days before had fed upon a mild case of yellow fever in the fifth day of his disease, the fact that no infection resulted, for Lazear continued in excellent health for a space of time far beyond the usual period of incubation, served to discredit the mosquito theory in the opinion of the investigators to a degree almost beyond redemption.

This state of things, the gradual loss of faith in the danger which mosquitoes seemed to possess, led Dr. Lazear to relax a little and become less scrupulous in his care of the insects and often, applying them to patients, if pressed for time, he would take them away with him to his laboratory at Columbia Barracks, where, the season being then quite warm, they could be kept as comfortably as at the Military Hospital laboratory. Thus it happened that on the twenty-seventh of August he had spent the whole morning at "Las Animas" Hospital getting his mosquitoes to take yellow fever blood, this rather tedious work, on that day, lasted until nearly the noon hour, so that Lazear, instead of leaving the tubes at the Military Hospital, took them all with him to Camp Columbia, among them was one insect that for some reason or other had failed to take blood when offered it at the hospital.

This mosquito had been hatched at the laboratory and in due time fed upon yellow fever blood from a severe case, twelve days before, the patient then being in the second day of his illness, also at three other times, six

days, four days and two days before. Of course, at the time, no particular attention had been drawn to this insect, except that it refused to suck blood when tempted that morning.

After luncheon that day, as Carroll and Lazear were in the laboratory attending to their respective work, the conversation turning upon the mosquitoes and their apparent harmlessness, Lazear remarked how one of them had failed to take blood, at which Carroll thought that he might try to feed it, as otherwise it was liable to die before the next day, (the insect seemed weak and tired), the tube was carefully held, first by Lazear and then by Carroll himself, for a considerable length of time, upon his forearm, before the mosquito decided to introduce its proboscis.

This insect was again fed from a yellow fever case at "Las Animas" Hospital on the twenty-ninth, two days later, Dr. Carroll being present though not feeling very well, as it was afterwards ascertained.

We three left the yellow fever hospital together that afternoon, on the following day, Lazear telephoned to me in the evening to say that Carroll was down with a chill after a sea bath taken a mile and a half from Camp and that they suspected he had malaria, we therefore made an appointment to examine his blood together the following morning.

When I reached Camp Columbia the morning of August 31, I found that Carroll had already been examining his own blood, not finding any malarial parasites, he told me he thought he had "caught cold" at the beach, his suffused face, blood-shot eyes and gen-

eral appearance, in spite of his efforts at gaiety and unconcern, shocked me beyond words. The possibility of his having yellow fever did not occur to him just then, when it did, two days later he declared he must have caught it at my autopsy room in the Military Hospital, or at "Las Animas" Hospital, where he had been two days before taking sick.

When we realized that Carroll had yellow fever we searched in our minds for all possibilities that might throw the blame of his infection upon any other source than the mosquito that bit him four days before. Lazear, as he related to me the details of Carroll's mosquito experiment, in his desire to exculpate himself, repeatedly mentioned the fact that he himself had been bitten two days before, without any effect therefrom and finally what seemed to relieve his mind to some extent was the thought that Carroll offered himself to feed the mosquito and that he held the tube upon his own arm until the work was consummated. We there and then decided to test the same mosquito upon the first non-immune person who should offer himself to be bitten, this was of common occurrence and taken much as a joke among the soldiers about the military hospital. An hour had not transpired before we had obtained our purpose. As Lazear stood at the door of the laboratory trying to "coax" the mosquito from one tube into another, a soldier who was strolling by stopped to observe the performance, upon being asked, he declared that he did not believe in the possible risk of mosquito bites and offered himself almost spontaneously, as several mosquitoes

took blood from his forearm, I noted on a slip of paper the necessary data.

William H. Dean, American by birth, belonging to Troop B, Seventh Cavalry, he said he had never been in the Tropics before and had not left the military reservation for nearly two months. The conditions for a test case were quite ideal.

Five days later, when he came down with yellow fever and the diagnosis of his case was confirmed by Dr. Roger P. Ames, U. S. Army, then on duty at the hospital, we sent a cablegram to Maj. Reed, still in Washington, apprising him of the fact that the theory of the transmission of yellow fever by mosquitoes, which at first was so much doubted and the transcendental importance of which we could then barely appreciate, had indeed been confirmed.

Both Carroll and Dean made an uninterrupted recovery, but we were to undergo the severest moral trial, compared to which the fearful days of Carroll's sickness dwindle into insignificance.

On the morning of the 18th of September, Lazear complained that he was "feeling out of sorts." I saw him the next day with all the signs of a severe attack of yellow fever. He assured us that he had not experimented upon himself, that is, that he had not been bitten by any of the purposely infected mosquitoes.

After the case of Dean so clearly demonstrated the certainty of mosquito transmission, we had agreed not to tempt fate by trying any more upon ourselves, we felt that we had been called upon to accomplish such work as did not justify taking risks which



then seemed really unnecessary. 'This we impressed upon Maj. Reed when he joined us in October, and for this reason he was never bitten by infected mosquitoes

Lazear, during his illness told us, in his lucid moments, that five days before, at the yellow fever hospital, (Las Animas,) a mosquito had alighted on his hand and stung him, while he was engaged in feeding others from a patient, that it escaped before he could capture it, but that he entertained no fear from it, inasmuch as he had been bitten the month before and no infection had resulted therefrom

Tuesday, the 25th of September, 1900, saw the end of a life that had been full of promise, one more name, that of Jesse W. Lazear, was graven upon the portals of immortality

The state of mind in which this calamity left us cannot be adequately described. The arrival of Maj. Reed several days after in a great measure helped to relieve the tension of our nerves and render us a degree of moral support of which we were sorely in need

We fully realized that three cases, two experimental and one accidental, were not sufficient proof, and that the medical world was sure to look with doubt upon any opinion based on such meager evidence, besides, in the case of Carroll, we had been unable to exclude the possibility of other means of infection, so that we really had but one indisputable case, Dean's, that we could present. In spite of this, we thought that the results warranted their presentation in the shape of a "Preliminary Note" and after the data were carefully collected from Lazear's

records and those at the Military Hospital, a short paper was prepared which the Major had the privilege of reading at the meeting of the American Public Health Association, held on October 24th, in the city of Indianapolis

For this purpose Maj. Reed went to the States two weeks after his return to Cuba and Carroll took a short vacation so as to fully recuperate, in preparation for the second series of inoculations which we had arranged to undertake, after the Indianapolis meeting, upon volunteers who, with full knowledge of the risks involved, would consent to suffer a period of previous quarantine

Let us look for a moment into the origin of the mosquito theory

The possible agency of insects in the propagation of yellow fever was thought of by more than one observer, from a very early period in the history of this disease. For instance, Rush, of Philadelphia, in 1797, noticed the excessive abundance of mosquitoes during that awful epidemic. Subsequently, several others spoke of the coincidence of gnats or mosquitoes and yellow fever but without ascribing any direct relation of the one regarding the other. Of course, man-to-man infection through the sole intervention of an insect was a thing entirely inconceivable and therefore unthought of until very recently, and in truth, the discovery, as far as yellow fever is concerned, was the result of a slow process of evolution of the fundamental fact, taken in connection with similar findings in other diseases

The earliest direct reference is found in the writings of Dr. Nott, of Mobile, Ala., who in 1848 suggested

that the dissemination of the yellow fever poison was evidently by means of some insect "that remained very close to the ground" But the first who positively pointed to the mosquito as the spreader of yellow fever, who showed that absence of mosquitoes precluded the existence of the disease and who prescribed the ready means to stamp it out by fumigation and by preventing the bites of the insects, was Dr Louis D Beauperrhuy, a French physician, then located in Venezuela I have an original copy of his paper, published in 1853, where he fastens the guilt upon the mosquitoes, believing, in accord with the prevailing teachings of the time, that they infected themselves by contact or feeding upon the organic matter found in the stagnant waters where they are hatched, afterwards inoculating the victims with their stings He recognized the fact that yellow fever is not contagious and therefore could not think of the possibility of man-to-man infection, as we know it today No one believed him, and the commission appointed to report upon his views said that they were inadmissible and all but declared him insane

This field of investigation remained dormant for a comparatively long period of time Meanwhile, another medical writer, Dr Greenville Dowell, mentions in 1876, that "if we compare the effect of heat and cold on gnats and mosquitoes with yellow fever, it will be difficult to believe it is not of the same nature, as it is controlled by the same natural laws" Soon after this, in 1879, the first conclusive proof of the direct transmission of a disease from man to man was presented by

the father of Tropical Medicine, Sir Patrick Manson, with regard to filaria, which the mosquito, as you know, takes from man and after a short time may pass it over to another subject This discovery attracted world-wide attention and many looked again towards the innumerable species of biting insects that dwell in the Tropic Zone, as possible carriers of the obscure diseases which also prevail in those regions

In 1881, Dr Carlos J Finlay, of Havana, in an exhaustive paper read before the Royal Academy of Sciences, gave as his opinion that yellow fever was spread by the bites of mosquitoes, "directly contaminated by stinging a yellow fever patient, (or perhaps by contact with or feeding from his discharges)" This view he held as late as 1900, which although correct in the main fact of the transmission of the germ from a patient to a susceptible person by the mosquito, the *modus operandi*, as he conceived it, was erroneous Dr Finlay, unfortunately, was unable to produce experimentally a single case of fever that could withstand the mildest criticism, so that at the time when the Army Board came to investigate the causes of yellow fever in Cuba his theory, though practically the correct one, had been so much discredited, that the best known experts considered it as an ingenious but wholly fanciful one

The important discoveries of Theobald Smith, as to the agency of ticks in spreading Texas fever of cattle, and those of Ross and the Italian investigators who showed conclusively that malaria was transmitted by a species of mosquito, brought the

knowledge of these various diseases to the point where the Army Board took up the investigation of yellow fever

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Perhaps I have gone too minutely into the manner in which the first series of mosquito infections took place under our hands and I hope it was not too wearisome to most of my hearers, but there were several points, not brought out in the strictly technical articles prepared at the time, which I thought should be put on record for the benefit of future historians

The second and final series of experiments were made possible thanks to the public spirit and the moral support of Governor General Leonard Wood and by his appropriation of funds for the purpose

An experimental camp was established and sufficiently safeguarded and there the men in small groups were brought in, kept under quarantine from eight to ten days, selecting only young healthy adults for the experiments, after they signed a document where they stated their willingness in spite of the possible risk incurred, always receiving an amount of money for their consent, with the three notable exceptions later explained

In this, Camp Lazear, so named in honor to the memory of our departed colleague, besides the tents necessary for the men and guard, two small frame buildings, properly screened against mosquitoes, were erected

Feeling that we had proved, to ourselves at least, the agency of the mosquito in yellow fever, it became our duty to disprove the theory, until then held as a certainty by many authori-

ties, to the effect that the soiled bedding and clothing, the secretions and excreta of patients, were infectious and in some way carried the germ of the disease. We therefore utilized one of the small wooden buildings, with a capacity of 2,800 cubic feet. The walls and ceiling were absolutely tight, the windows and vestibuled door duly screened and all precautions taken to prevent the entrance of insects

Into this room a stove, to maintain a high tropical temperature, was introduced, also three beds, mattresses and pillows, underwear, pajamas, towels, sheets, blankets, etc., soiled with blood and discharges from yellow fever cases, these articles were put on the beds, hung about the room and packed in a trunk and two boxes placed there for the purpose

The building was finished and equipped on November 30th. That Friday evening, Dr Robert P. Cook, U S Army, with two other American volunteers entered it and prepared to pass the night, they had instructions to unpack the boxes and the trunk, to handle and shake the clothing and in every way to attempt to disseminate the yellow fever virus, in case it were contained in the various pieces. We watched the proceedings from the outside, through one of the windows. The foul conditions which developed upon opening the trunk were of such a character that the three men were compelled to rush out of the building into the fresh air, yet, after a few minutes, with a courage and determination worthy only of such a cause, they went back and passed a more or less sleepless night, in the midst of an indescribably filthy environment

For twenty consecutive nights these men went through the same performance, during the day they remained together, occupying a tent near their sleeping quarters. Dr Cook, by voluntarily undergoing such a test, without any remuneration whatsoever, proved his faith in the mosquito theory, his demonstration of the harmless character of so-called infected clothing in yellow fever has been of the greatest importance.

A considerable number of enlisted men were anxious to submit themselves to the mosquito bites and thus aid in solving the mystery of yellow fever. Two particular cases require special mention. John R. Kissinger, a private in the Hospital Corps of the Army, was the first to offer himself, without any desire of pecuniary or other consideration and solely "in the interest of humanity and the cause of science", the other, J. J. Moran, a civilian employe also stipulated as a condition that he was to receive no pay for his services. Both these men, in due time, suffered from yellow fever and until very recently had never obtained any reward for the great risk which they ran so voluntarily and praiseworthy.

Kissinger became infected by having mosquitoes applied to him, while Moran obtained his yellow fever by lying down in the "infected mosquito building" and being bitten, of course, by several insects set free in the room for the purpose.

All the other cases in the persons of Spanish volunteers were produced by the bites of infected mosquitoes. After these experiments showed conclusively the transmission of the dis-

ease in this manner, it was produced also by the direct injection of yellow fever patients' blood subcutaneously, and later by blood serum that had been filtered through a Berkefeld bougie.

These experiments did not cause a single death.

The work of the Board showed,

- 1 That yellow fever is transmitted by the sting of mosquitoes now called *Aedes aegypti*,
- 2 That the mosquito becomes infected only when it stings the yellow fever patient during the first three days, possibly four days, of the disease,
- 3 That the mosquito becomes infective only after the 10th day, in Winter probably the 12th day, of taking the blood from the yellow fever patient,
- 4 That the period of incubation in man does not extend beyond six days,
- 5 That articles of clothing or excreta of yellow fever patients are not infective.

Since we made our demonstration in 1901, our work has been corroborated by various committees appointed for the purpose, in Cuba, Mexico and Brazil, composed variously of American, French, English, Cuban, Brazilian and German investigators. Nothing has been added to our original findings, nothing has been contradicted of what we have reported, and today, after twenty-seven years, the truths that we uncovered stand incontrovertible, besides they have been the means of stamping out yellow fever from

Cuba, the United States, (Laredo, Tex, 1903, and New Orleans, La, 1905,) British Honduras, Ecuador, Panama, Salvador, Colombia and most of Brazil

The causative agent, the parasite of yellow fever, remains unknown in spite of the most commendable work later undertaken by Beyer, Pothier and Parker in Vera Cruz, (1902), Seidelin in Yucatan, (1911), and Noguchi in Ecuador, Mexico and Brazil, (1919 to date)

The *Leptospira icteroïdes* which, on

epidemiologic grounds could not be accepted as the etiologic factor in yellow fever, has been identified as a twin brother of the leptospira of Weil's disease and shall soon, it is to be deplored, as occurred with *Bacillus icteroïdes*, disappear from further consideration in this connection

Without the discovery of the germ, as is the case with rabies, yellow fever is now under control and I am confident that, for the good of mankind, it will finally be exterminated

Havana, February, 1928

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# Metadysentery\*

By ALDO CASTELLANI, M.D., Professor of Tropical Medicine, Tulane University of Louisiana, New Orleans

SOME years ago I introduced a new classification of bacterial dysenteries as follows

- 1 *Bacterial dysentery sensu stricto* (synonyms Shiga dysentery, Shiga-Kruse dysentery), due to dysentery organisms which do not ferment lactose or mannitol and do not clot milk (*Shiga-Kruse bacillus*)
- 2 *Paradysentery*, due to organisms which do not ferment lactose, ferment mannitol (acid only), do not clot milk (Flexner, Hiss--Russell, etc.)
- 3 *Metadysentery*, due to organisms, the metadysenteric bacilli, which, as is the case with the true dysentery bacilli, do not produce gas in any sugar, but either ferment lactose (acid only) and clot milk or ferment lactose (acid only) without clotting milk, or clot milk without fermenting lactose (*Organisms of the genus Dysenteroides and Lankoides*)

To make clear this grouping of bacterial dysenteries and dysentery bacilli, it is necessary to say a few words

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on the classification of the aerobic (facultative anaerobic) asporigenous, non-capsulated, gram-negative intestinal bacilli which do not liquefy gelatine or serum and do not produce pigment, viz, the tribe *Ebertheae* of Chalmers and myself, "Bacillaceae growing well on ordinary media, not forming endospores, aerobes and often facultative anaerobes, without fluorescence, pigment formation or gelatine liquefaction, without polar-staining, gram-negative, without a capsule"

The tribe *Ebertheae* may be subdivided into two subtribes

- (a) The organisms do not produce gas in glucose or any other sugar — Subtribe *Eberthoanaerogeneae*
- (b) The organisms produce gas in glucose and usually in other sugars — *Ebertho-aerogeneae*

The first subtribe contains six genera

- 1 *Alkaligenes* Castellani and Chalmers
- 2 *Vibriothrix* Castellani
- 3 *Eberthus* Castellani and Chalmers
- 4 *Shigella* Castellani and Chalmers
- 5 *Lankoides* Castellani and Chalmers

- 6 *Dysenteroides* Castellani and Chalmers

The second subtribe contains five genera

- 1 *Salmonella* Lignières
- 2 *Wesenbergus* Castellani and Chalmers
- 3 *Enteroides* Castellani and Chalmers
- 4 *Balkanella* Castellani and Chalmers
- 5 *Escherichia* Castellani and Chalmers

These eleven genera can be easily differentiated by using three media milk, lactose, and glucose

- 1 Genus *Alkaligenes*—Milk not clotted, (no change in the reaction of the medium, or alkaline), Lactose, no gas, (no change, or alkaline), Glucose, no gas (no change in the reaction of the medium, or alkaline)
- 2 Genus *Vibriothrix*—Same reactions as *Alkaligenes*, but the organisms of this genus are very polymorphic, vibrio-like, spirillum-like, bacillus-like, all the different forms may be found in the same preparation, they probably belong to the Higher Fungi (see Castellani and Chalmers' "Manual of Tropical Medicine," 3rd edition, p 1068)
- 3 Genus *Eberthus*—Milk not clotted, Lactose no change, Glucose Acid, motility +
- 4 Genus *Shigella*—Same characters as *Eberthus* but motility 0

- 5 Genus *Dysenteroides*—Milk not clotted, Lactose Acid, Glucose Acid

- 6 Genus *Salmonella*—Milk not clotted Lactose no change, Glucose Acid and Gas
- 7 Genus *Wesenbergus*—Milk not clotted, Lactose Acid, Glucose Acid and Gas
- 8 Genus *Enteroides*—Milk not clotted, Lactose Acid and Gas, Glucose Acid and Gas
- 9 Genus *Lankoides*—Milk clotted (very slowly), Lactose no change or slowly acid, Glucose Acid
- 10 Genus *Balkanella*—Milk clotted, Lactose Acid or no change, Glucose Acid and Gas
- 11 Genus *Escherichia*—Milk clotted, Lactose Acid and Gas, Glucose Acid and Gas

The differential biochemical characters of the above genera are summarized in Table I

*Classification of the Dysentery Bacilli*—The dysentery bacilli, according to the classification of Chalmers and myself, belong to the following three genera *Shigella*, *Dysenteroides*, and *Lankoides*, of the tribe *Ebertheae*, subtribe *Eberthoanaerogeneae*. It may be of advantage perhaps to deal with these genera in a more detailed manner

Genus *Shigella* Castellani and Chalmers, 1918

*Definition*—*Ebertheae* not fermenting lactose, glucose partially fermented with production of acid but no gas Milk not clotted Motility absent

Type Species—*S. dysenteriae* Shiga-Kruse, 1899

Classification—Several species have been described but the two generally admitted as valid are the following

- 1 *S. dysenteriae* Shiga-Kruse
- 2 *S. paradysenteriae* Collins

The two species are differentiated by their behavior in mannitol. *S. dysenteriae* does not produce acidity, *S. paradysenteriae* produces acidity. Of *S. paradysenteriae* Collins there are several varieties: Var *Flexneri*, Var *Hissi-Russelli*, Var *Strongi*, Var *Duvali* etc. The two best known are

- 1 *S. paradysenteriae* Collins Var *Flexneri* (so-called Flexner bacillus)
- 2 *S. paradysenteriae* Collins Var *Hissi-Russelli* (so-called Y bacillus)

The two varieties are differentiated by their reactions in maltose, the Flexner variety produces acidity in maltose, the Hiss-Russell variety does not produce acidity in maltose. I have found that they differ also with regard to their reactions on starches, the Var *Flexneri* produces acidity in potato and ginger, the Var *Hissi-Russelli* does not touch those two starches.

Differentiation of *S. dysenteriae* Shiga-Kruse, *S. paradysenteriae* Collins Var *Flexneri*, and *S. paradysenteriae* Collins Var *Hissi-Russelli* by means of the Symbiotic Fermentation Phenomenon—The symbiotic fermentation phenomenon has been described by me in previous publications. It may be defined as follows: "Two organisms neither of which alone produces gas in certain carbohydrates may do so when living in symbiosis or artificially mixed." For instance, *B. typhosus* alone does not produce gas in maltose (acid only), *B. Morganii* does not produce gas in that sugar (neither acid nor gas, the mixture *B. typhosus* + *B. Morganii* produces gas. The phenomenon, as I have shown in other publications, may be of assistance in the classification of certain bacteria. The more important dysentery bacilli of the genus *Shigella* may be differentiated as follows: The symbiosis *B. dysenteriae* Shiga-Kruse + *B. Morganii* produces gas in maltose but not in mannitol, the symbiosis *B. paradysenteriae* Var *Flexneri* + *B. Morganii* produces gas in maltose and mannitol, the symbiosis *B. paradysenteriae* Var *Hissi-Russelli* + *B. Morganii* produces gas in mannitol but not in maltose.

TABLE III

Differentiation between *B. dysenteriae* Shiga-Kruse, *B. paradysenteriae* Collins Var *Flexneri*, and *B. paradysenteriae* Collins Var *Hissi-Russelli* by Their Fermentative Action on Mannitol and Maltose

	Mannitol	Maltose	Remarks
Shiga-Kruse	O	AVS	Production of acid very slow
Flexner	A	A	
Y (Hiss-Russell)	A	O	

O = Absence of acidity and gas  
 A = acidity present  
 G = gas present  
 VS = Very slight



TABLE I  
TRIBE EBERTHEAE

GENUS	LITMUS MILK	LACTOSE	GLUCOSE	REMARKS
Alkaligenes	O (Alk)	O (Alk)	O (Alk)	Same biochemical reactions as Alkaligenes but organisms are polymorphic, bacillus-like, vibrio-like and undulating filaments are often present in the same preparation Probably belong to Higher Fungi (see Castellani and Chalmers' "Manual of Tropical Medicine," p 1,068)
Vibriothrix	O (Alk)	O (Alk)	O (Alk)	
Eberthus	O	O	A	Motility present
Shigella	O	O	A	Same biochemical reactions as Eberthus, but the organisms are non-motile
Dysenteroides	O	A	A	
Salmonella	O	O	AG	
Wesenbergus	O	A	AG	
Enteroides	O	AG	AG	
Lankoides	C (slowly)	O or A	A	
Balkanella	C	O or A	AG	
Escherichia	C	AG	AG	

O = Negative, viz , absence of clotting in milk, absence of acidity and gas in sugar media  
A = Acid  
AG = Acid and gas  
Alk = Strongly alkaline  
C = Milk clotted

*Key for the Identification of the Genera of the Tribe Ebertheae*

The following key may be found useful for the generic identification of intestinal organisms of the tribe *Ebertheae*, viz , non-capsulated, gram-negative, non-sporigenous bacilli which grow well on agar, are aerobic (faculative anaerobic), do not produce pigment, do not liquefy gelatine or serum

TABLE II  
KEY TO THE GENERA OF THE TRIBE EBERTHIAE  
So-called Alkaligenes, Typhoid-Dysentery, Paratyphoid, Coli Groups of Bacteria

EBERTHAE—GAS IN GLUCOSE (Intestinal, non-capsu- lated bacilli, which are aerobic [facultative an- aerobic], grow well on agar, do not produce pigment, are non-spori- genous, non bipolar staining, gram-nega- tive, gelatine and ser- um not liquefied)	Not clotted— Acidity in glucose		Clotted Lankoides	
	Gas absent (O) SUBTRIBE EBERTHOANAERO- GENEAE—MILK		Gas present(+) SUBTRIBE EBERTHOAERO- GENEAE—MILK	
	Absent (O or Alk)		Present (A) — Lactose	
	bacillus, Alkaligenes		pleomorphic (bacillus, vibrio, spirillum) Vibriothrix	
	O, motility		O, motility { +, Eberthus O, Shigella—Mannitol	
	A, Dysenteroides		O, Dysentery type <i>sensu stricto</i>	
			A, Paratyphoid type—maltose	
			Shiga Kruse A, Flevner type O, Y (Hiss- Russell type)	
	Not clotted— Lactose		O, Salmonella—Maltose	
			A, Wesenbergus	
			AG, Enteroides	
			O, Morgan group	
			+ Saccharose	
			O, Paratyphoid group <i>sensu lato</i>	
			+ Asiaticus group	
	Clotted— Lactose		A or O, Balkanella	
			AG, Escherichia— Saccharose	
			+ Section communior	
			O, Section communis	

O = Negative result, viz, absence of clotting in milk, absence of acidity and gas in sugar media  
+ = Positive, viz, presence of clotting in milk, presence of acid and gas in sugar media  
A = Acid  
G = Gas  
AG = Acid and gas  
Alk = Strongly alkaline



TABLE V  
GENUS SHIGELLA  
Castellani and Chalmers, 1918  
(Reactions after an Incubation Period at 37° C for 15 Days)

	Motility	Gram	Gelatin	Serum	Litmus Milk	Lactose	Glucose	Levulose	Maltose	Galactose	Mannitol	Dulcitol	Saccharose	Inulin	Isodulcitol	Inositol	Adonitol	Arabinose	Amygdalin	Salicin	Sorbitol	Raffinose	Dextrin	Erythritol	Glycerin	Ginger	Potato	Rice Starch	Indol	Production of acid in maltose very slow	Differs from B dysenteriae Shiga in fermenting saccharose and in producing indol	Not agglutinated by Shiga Kruse serum	Not agglutinated by Shiga-Kruse serum
S dysenteriae Shiga Kruse	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+			
S lunavensis Castellani 1912	0	0	0	0	As	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
S negombensis Castellani 1910	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+			
S paradysenterica Castellani 1904	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+			
S paradysenteriae Collins Var Flexneri	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+			
S paradysenteriae Collins Var Hiss-Russelli.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+			
S paradysenteriae Collins Var Strongi	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+			
S tangellensis Castellani 1911	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
S metafaecaloides Castellani	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			

As = Acid, slightly  
Avs = Acid, very slightly  
AG = Acid and gas

O = No change, viz., absence of clotting in milk, absence of acidity and gas in sugar media  
+ = Positive, viz., presence of clotting in milk, presence of acid and gas in sugar media, etc  
ALK = Alkaline

As = Acid, slightly  
Avs = Acid, very slightly  
AG = Acid and gas

O = No change, viz., absence of clotting in milk, absence of acidity and gas in sugar media  
+ = Positive, viz., presence of clotting in milk, presence of acid and gas in sugar media, etc  
ALK = Alkane

capable of fermenting many more sugars. For instance, most strains of *B. ceylonensis* A and *B. guntottensis* will give acidity in very many more sugars than those mentioned in our key and table if incubated for over a week, moreover, some strains serologically true may produce acidity in numerous carbohydrates even after a short incubation. The best way of differentiating the various species is therefore by serological methods. The study of their fermentative reactions (both simple and by using symbiotic fermentative reactions) may, however, be helpful in some cases.

From a practical point of view the organisms of the *Lankoides* group may be separated into two principal types —

*L. ceylonensis* "B" type—indol positive, production of acidity in lactose usually fairly rapid.

*L. ceylonensis* "A" type—indol negative, production of acidity in lactose very slow, or absent. Clotting of milk may be extremely slow, taking 3 or 4 weeks.

Of each type there are several sub-types or varieties which are best differentiated serologically.

*Inoculation in the lower animals* —  
*Serological reactions* —Peptone water and broth culture of *Lankoides ceylonensis* "B" Strain RR, *Lankoides ceylonensis* "B", Strain RW, *Lankoides ceylonensis* "B", Strain O, inoculated subcutaneously (1 cc -2 cc) in rabbits, do not, as a rule, produce severe symptoms, although there are exceptions. Agglutinins are produced in a fair amount. The rabbits inoculated with

any of the three strains of *L. ceylonensis* "B" will produce agglutinins for the homologous strain and for the other two strains of *L. ceylonensis* "B" in practically the same amount, as a rule, there is no agglutination for any strain of *L. ceylonensis* "A" or only slight, *L. ceylonensis* "A" serum does not agglutinate or only slightly strains of *L. ceylonensis* "B". *L. ceylonensis* "B" serum and *L. ceylonensis* "A" serum do not agglutinate *Lankoides madampensis*.

Genus *Dysenteroides* Castellani and Chalmers, 1918

*Definition* —Ebertheae fermenting lactose and glucose partially with the production of acid but no gas, milk not clotted.

*Type Species* —*Dysenteroides metadysentericus* (Castellani, 1907). The first strain of this organism was isolated in 1904, but was not named for some years.

*Remarks* —This genus contains several organisms, one motile (*D. bentonensis*) and several non-motile, *D. metadysentericus* "A", *D. metadysentericus* "B", *D. metadysentericus* "C", *D. metadysentericus* "D", which Chalmers and I differentiated by their sugar reactions. These varieties, however, are better separated by serological methods, as the sugar reactions have a rather marked tendency to vary. It must also be noted that a number of strains which at first appear as belonging to this genus, belong, in reality, to the Genus *Lankoides*, these strains, if kept in the incubator at 37° C for less than two weeks will not clot milk, but if they are kept un-

TABLE VI  
GENUS LAKKOIDS  
Castellani and Chalmers  
(Reactions after an Incubation Period at 37° C for Three Weeks)

	Motility	Gram	Gelatine	Serum	Litmus Milk	Lactose	Glucose	Levulose	Maltose	Galactose	Mannitol	Dulcitol	Saccharose	Inulin	Isodulcitol	Inositol	Adonitol	Arabinose	Amygdalin	Silicin	Sorbitol	Raffinose	Dextrin	Erythrite	Glycerine	Starch (Potato)	Indol	Lead Agar	REMARKS		
<i>L. ceylonensis</i> "B" Castellani 1907 (Strain RR)	O	O	O	O	AC	A	A	A	A	A	A	A	A	O	or	O	O	O	A	O	O	A	A	O	A	O	A	+	O		The four strains of <i>B. ceylonensis</i> B are serologically identical, strains RR and O produce acidity in lactose rapidly, strain RW very slowly
<i>L. ceylonensis</i> "B" Castellani 1907 (Strain RW)	O	O	O	O	AC	As	A	A	A	A	A	A	A	O	or	O	O	O	A	O	O	A	O	O	A	A	+	O			
<i>L. ceylonensis</i> "B" Castellani 1907 (Strain LV)	O	O	O	O	AC	A	A	A	A	A	A	A	A	O	or	O	O	O	A	O	O	A	A	O	1	A	+	O			
<i>L. ceylonensis</i> "B" Castellani 1907 (Strain O)	O	O	O	O	AC	A	A	A	A	A	A	A	A	O	or	O	O	O	A	O	O	A	A	O	A	A	+	O			
<i>L. ceylonensis</i> "A" Castellani 1907 (Strain PD)	O	O	O	O	AC	AVS	A	A	A	A	A	A	A	O	or	O	O	O	A	O	O	O	A	AS	O	A	O	O	O		Some strains of <i>B. ceylonensis</i> A at first produce acid in Glucose only, lactose is not fermented, or only very slowly, milk is clotted very slowly
<i>L. ceylonensis</i> "A" Castellani 1907 (Strain O)	O	O	O	O	AC	O	A	A	A	A	A	A	A	O	or	O	O	O	A	O	O	O	A	AVS	O	A	O	O	—		
<i>L. ceylonensis</i> "A" Castellani 1907 (Strain Z)	O	O	O	O	AC	A	A	A	A	A	A	A	A	O	or	O	O	O	A	O	O	O	A	O	O	A	O	O	O		
<i>L. madampensis</i> Castellani 1911 (Strain H)	O	O	O	O	AC	A	A	A	A	A	A	A	AS	O	or	O	O	O	A	O	O	AVS	A	A	O	A	O	+	O		
<i>L. pyogenes foetidus</i> Passet 1902	+	O	O	O	AC	A	A	A	A	A	A	A	A	—	—	—	—	A	—	—	—	A	—	—	—	—	—	+			

O = Negative, viz., absence of clotting in milk, absence of acidity and gas in sugar media (medium may become alkaline)  
+ = Positive, viz., presence of clotting in milk, presence of acidity and gas in sugar media, etc

A = Acid

C = Milk clotted

AS = Acid, slightly

AVS = Acid, very slightly

The four strains of *B. ceylonensis* B are serologically identical, strains RR and O produce acidity in lactose rapidly, strain RW very slowly

Some strains of *B. ceylonensis* A at first produce acid in glucose only, lactose is not fermented, or only very slowly, milk is clotted very slowly

der observation for more than two or three weeks their reactions are those of the genus *Lankoides*, milk becoming clotted

*Animal Experiments—Toxic Action on Rabbits*—When broth or peptone water cultures are injected in ordinary doses ( $\frac{1}{2}$  to 1 cc) most strains are not toxic. Olivi, with a strain of *B metadysentericus*, induced the death of a rabbit 5 days after a single injection of a 3 cc dose, while rabbits inoculated with 2 or 1 cc did not die. In the rabbits that died, the post-mortem showed inflammatory lesions similar to those found in rabbits inoculated with Shiga-Kruse

Remarks on the Bacilli of the Genus  
*Lankoides* and of the Genus *Dys-*  
*enteroides* (Metadysentery  
Bacilli)

In practice it is useful to combine the two genera *Lankoides* and *Dysenteroides* into one group the *Lankoides--Dysenteroides* group, or *Dysenteroides sensu lato*, or "metadysentery bacilli", because certain organisms which at first present the characters of the genus *Dysenteroides* after a prolonged incubation may show the characters of the genus *Lankoides*, viz, they will clot milk

The "metadysentery bacilli" (*Lankoides-Dysenteroides* group) are similar to the dysentery bacilli *sensu stricto* (genus *Shigella*, "dysentery-paradysentery" bacilli) in that they do not produce gas in any sugar, they differ from them however, as they either produce acidity in lactose and clot milk or produce acidity in lactose without clotting milk, or they clot milk

without producing distinct acidity in lactose. Some of these bacilli have been known for years, *Bacillus ceylonensis* "A" and "B" were found by me in 1904 and 1905, their full description being published in 1907, and I isolated a strain as long ago as 1901, although it was not classified at the time—it is still in my collection. *B guntottensis* I described in 1910, *B madampensis* I isolated in 1910 and described in 1911, the first strain of *B metadysentericus* was isolated in 1904, but was not named for some years. Chalmers and I created for these organisms two genera *Lankoides* and *Dysenteroides*. Nabarro has given much attention to this group of organisms, he is inclined to identify them all with *B coli anaerogenes* of Lembke, and in a very interesting publication in the "Journal of Pathology and Bacteriology," 1923, vol. xxvi, pages 429-430, states the following

"Lembke in 1896 isolated from the excreta of dogs a coliform bacillus producing acid but not gas in glucose and lactose media, to which he gave the name *B coli anaerogenes*. Between 1905 and 1912 Castellani isolated several varieties in Ceylon which he has named *B ceylonensis*, *B madampensis*, *B bentotensis*. These organisms all agree in the property of fermenting sugars, etc, with the formation of acid alone, the difference between them being of a minor nature"

Nabarro further states that he first isolated *B coli anaerogenes* in 1912 from a case of dysentery at the Wakefield Asylum. In 1921 during an in-

## Metadysentery

TABLE VII  
GENUS DYSENTEROIDES

GENUS DYSENTERIOIDES																											
	Motility	Gram	Gelatine	Serum	Litmus Milk	Lactose	Glucose	Levulose	Maltose	Galactose	Mannitol	Dulcitol	Saccharose	Inulin	Isodulcitol	Inositol	Adonitol	Arabinose	Amygdalin	Salicin	Sorbitol	Raffinose	Dextrin	Erythrite	Glycerine	Portno Starch	Indol
<i>D metadysentericus</i> Castellani Var "A"	O	O	O	O	A	A	A	A	A	AS	A	AS or	A	O	—	—	—	—	—	—	—	—	—	—	—	—	+
<i>D metadysentericus</i> Castellani Var "A" (Strain Z)	O	O	O	O	A	A	A	A	A	A	A or	O	AS or	O	A	O	O	O	A	O	O	A	O	O	O	O	O
<i>D metadysentericus</i> Castellani Var "B" (Strain L)	O	O	O	O	A	A	A	A	A	A	AS or	O	AS or	O	AS or	O	O	A	O	O	O	A	A	O	A	—	+
<i>D metadysentericus</i> Castellani Var "C"	O	O	O	O	A	ALK	AS	A	AS	A	AS or	AVS	AVS	AVS	—	—	—	—	—	—	—	—	—	—	—	—	O
<i>D metadysentericus</i> Castellani Var "D"	O	O	O	O	ALK	AS	A	A	A	A	A	A	A	A	—	—	—	—	—	—	—	—	—	—	—	—	+
<i>D metadysentericus</i> Castellani Var "D"	+	O	O	O	A,ALK	A	A	A	A	A	O	AS or	AS	A	O	O	A	O	O	O	AS or	O	AS or	O	O	A	+
<i>D bentotensis</i> Castellani																											

(the medium may become alkaline)

O = Negative, viz., absence of clotting in milk, absence of acidity and gas in sugar media (the medium may become alkaline)  
 + = Positive, viz., presence of clotting in milk, presence of acid and gas in sugar media, etc

A = Acid  
 AB = Acid and gas  
 ALK = Alkaline  
 — = Reaction unknown  
 AS = Acid, slightly  
 AVS = Acid, very slightly  
 D = Decolorized



vestigation upon summer diarrhea and other diarrheal conditions in children, he isolated 30 strains of *B coli anaerogenes* from 25 patients out of 107 investigated

There is much to be said in favor of Nabarro's theory that the anaerogenes bacilli isolated by me and later by himself, Sonne and others are identical with *B coli anaerogenes* of Lemke. As, however, since 1905, I have always found constant serological differences between the principal organisms of the group, I have retained in this paper in its general lines the classification introduced by Chalmers and myself

#### CLINICAL SYNDROMES ASSOCIATED WITH THE PRESENCE OF THE METADYSENTERY BACILLI

The clinical intestinal conditions in which organisms of the metadysentery bacilli have been isolated and for which the term "metadysentery" *sensu lato* (a term introduced by me some years ago) might be applied, may be classified as follows

- (a) *Acute*—With either dysenteric diarrhea or simple diarrhea
- (b) *Chronic*—Several types.

These organisms have also been found at times in obscure cases of fever in which intestinal symptoms may be very slight or lacking altogether

*Chronic Colitis associated with Organisms of the Metadysentery Group*—(Synonyms Chronic lankoides-dysenteroides colitis, chronic dysenteroides colitis, chronic metadysenteric colitis, chronic metadysentery)

In this paper I wish to discuss a chronic type characterized by recurrent attacks of simple diarrhea with absence or only occasional presence of dysenteric symptoms. The stools during the attack are fluid, brownish or yellow, at times frothy, as a rule they do not contain muco-pus or blood, but there are a number of exceptions. Each attack may begin suddenly with severe abdominal pain, or only abdominal discomfort may be felt, it lasts from a few hours to several days. In the intervals between the attacks, and the intervals may be very prolonged, the patient may feel fairly well, but as a rule complains at times of slight abdominal discomfort and flatulency, he often feels run down, tired, nervous and not inclined for work. These cases go on for years, a little better, a little worse, they consult many practitioners, and are generally told they are suffering from "colitis" or "intestinal intoxication" or "intestinal sub-infection"; sometimes the diagnosis "mucous colitis" and "abdominal neurasthenia" is made. Not rarely atypical appendicitis is suspected and the patient is operated on. The patients try all sorts of treatment, Plombières douching being probably the most popular and next to it streptococcal vaccines and various so-called intestinal disinfectants. The result is generally unsatisfactory. Some of these patients have a wretched life and are a burden to themselves and their families

*Diagnosis*—This is difficult, the bacteriological examination of the stools may be negative very many times before metadysentery organisms are found. In the chronic cases what

I have found most helpful is testing the blood for agglutination for the principal varieties of the group. My routine procedure is to test the blood of every suspicious case for agglutination first of all for *B. ceylonensis* B, *B. ceylonensis* A and *B. metadysentericus* Z. When the agglutination is higher than 1 in 80, as a rule repeated bacteriological examinations of the stools will reveal sooner or later the presence of metadysentery organisms, although, as I have already stated, many examinations may have to be carried out before a successful one is obtained.

**Differential Diagnosis**—A very similar chronic clinical syndrome may be found caused by *E. histolytica*, also, though very rarely, by bacilli of the true dysenteric group (Shiga-Kruse and Flexner). Only repeated and thorough microscopical and bacteriological examinations will enable one to make a differential diagnosis.

**Illustrative Cases (recent cases)**—**Case I** Mrs. V. for the last two years has been suffering at intervals from attacks of diarrhea with severe abdominal pains, the stools being brownish or yellowish, at times somewhat frothy, never containing any blood. She came to consult me in June this year. A bacillus was isolated from the stools, with the characters of the bacilli of the genus *Lankoides*, viz., produced no gas in any sugar, produced acidity in lactose, clotted milk, slowly. The blood agglutinated the bacillus isolated from the stool up to a dilution of 1 in 160, and the laboratory strain of *B. ceylonensis* B up to a dilution of 1 in 120. The bacillus was not agglutinated by blood of normal individuals. A powerful Shiga serum (titre for Shiga), 1:1,000, obtained from Burroughs-Wellcome, agglutinated it only up to 1 in 20. The lady was admitted to a tropical nursing

home and was kept at complete rest in bed and on fluid diet. She had at first a dose of castor oil, and then bismuth and salol. A course of *Lankoides* vaccine (peptone water cultures killed by the addition of carbolic ½ per cent) was given in minute doses. She gradually got better, and up to the present day has not had any attacks. The agglutination for the bacillus isolated from the stools rapidly decreased, it is now negative.

**Case II**—Mrs. D., Englishwoman, had an acute attack of diarrhea with probably a little blood and mucus, 12 years ago in Rome. She did not go to see a doctor, and did not even go to bed, since then she has never been quite well. Very often she had abdominal discomfort and flatulency, as a rule, however, no diarrhea. She came to consult me in August, 1926, because she was passing through a period of reactivation with diarrhea, the stools being liquid of brownish colour.

A bacillus was isolated from the stool with all the characteristics of the *Lankoides* group, viz., slow clotting of milk, no production of gas in any sugar, acidity in glucose. I thought at first that lactose was negative, but after three weeks a slight amount of acid developed. Serologically the organism was identical with a strain of *B. ceylonensis* A isolated in Ceylon. The bacillus isolated from the stool was agglutinated by the patient's blood in a very high dilution of 1 in 3220, the laboratory strain of *B. ceylonensis* A was agglutinated in a dilution of 1 in 160.

**Case III** Mr. H. K. for the last two years has been suffering from attacks of diarrhea, with abdominal discomfort, apparently there was never any blood or mucus in the stools. He came to consult me in July of last year after a more than usually severe attack, he was still having three to six motions a day, which were liquid, somewhat frothy, and of a brownish colour. The examination of a stool passed by the patient in a sterile vessel in the laboratory showed absence of blood and pus, no amebae or flagellates present, no eggs of worms. A bacteriological exam-

ination was carried out in the usual way. On MacConkey's plates several white colonies appeared in addition to numerous red colonies. Some of the white colonies were further investigated, and a bacillus with all the characteristics of the one found in Case II was found (*B. ceylonensis* A). This bacillus was also serologically identical with the bacillus isolated in Case II. The patient refused to enter a nursing home owing to pressure of business, he was put on a strict diet, he took regularly some so-called intestinal disinfectants, and had a course of injections of vaccine prepared from his own bacillus. To date he has had no further attacks. The patient's blood agglutinated equally well (1:160) the bacillus isolated from the stool and the bacillus isolated from Case II. The agglutination limit for the laboratory strain of *Lankoides ceylonensis* A was 1:80.

*Case IV*—Mrs. H. has been suffering from rather obscure abdominal symptoms for many years, abdominal discomfort, flatulency, attacks of simple diarrhea with long periods of constipation, there was apparently at times slight tenderness in the right lower abdomen, appendicitis was suspected and an operation was performed. The appendix did not seem to be diseased. The lady came to consult me in August, 1926, merely complaining of vague abdominal discomfort and of always feeling tired and ill. The blood showed high agglutination (more than 1:160) both for *Lankoides ceylonensis* A and for *Lankoides ceylonensis* B, all strains, none for *Lankoides madampensis*.

*Bacteriological Investigation of Stools*—Three strains of *Lankoides* were isolated, one was agglutinated by the patient's blood and by *Lankoides ceylonensis* B serum, the third strain was not agglutinated by either the patient's serum or *Lankoides ceylonensis* A or *Lankoides ceylonensis* B sera. The third organism appeared to be identical with *Lankoides madampensis*. It would seem therefore, that in this case the condition was probably due to a mixed infection—

*Lankoides ceylonensis* B + *Lankoides ceylonensis* A.

*Case V*—Miss V., Australian, for the last ten years has been suffering from vague abdominal discomfort with occasional attacks of diarrhea, the stools never contained blood, according to her statements. She is somewhat nervous and anemic. The physical examination of the abdomen does not reveal anything abnormal. The bacterial examination of the stool shows presence of metadysentery bacilli, of the type *B. ceylonensis* A. The strain isolated from the stools is agglutinated by the patient's blood in a dilution of 1 in 320, the laboratory strains of *B. ceylonensis* A in a dilution of 1 in 80, the laboratory strain of *B. ceylonensis* B, 1 in 40, the laboratory strain of *B. dysenteriae*, Shiga-Kruse, is not agglutinated, the laboratory strain of *B. dysenteriae*, Flexner and Hiss-Russell, are agglutinated in a dilution of 1 in 10.

*Old Cases*—I may quote two cases given in a publication of mine in the *Journal of Hygiene* (vol. VII, No. 1, January, 1907).

(1) An Australian medical man, 24 years of age, arrived at Colombo from China in April, 1905. A week before reaching Colombo he began to feel ill with lassitude, headaches, diarrhea—10 to 15 motions daily with no mucus or blood—irregular low fever. The disease lasted two months. The diarrhea was followed by a long period of constipation. The convalescence was very prolonged, the patient suffering repeatedly from attacks of nervous tachycardia. A bacillus was isolated which clotted milk and produced acidity but no gas in many sugars, I gave a description of the bacillus and called it *B. ceylonensis* B. The original strain is still in my possession.

(2) A retired German officer. Strongly-built man, 50 years of age. No previous disease of any kind. Began to feel ill with malaise while on board a German steamer during the voyage from Aden to Colombo. Irregular rises of temperature, slight diarrhea. He never felt ill enough to remain in his cabin. As there was a

case of enteric on board, the same disease was suspected in this patient, and he was accordingly advised to land at Colombo. During the first three days after landing in Colombo he felt quite well and was getting ready to go up country when suddenly, in the afternoon, his temperature rose to 103.2°. There was slight shivering, severe headache, *diarrhea becoming a prominent symptom*, twelve liquid motions being passed in a few hours. I saw the patient in the evening temperature 102.4°, pulse 78, no roseola or any other rash, examination of the chest negative, spleen not enlarged, the stools, which were liquid and yellowish, did not contain blood or muco-pus. The fever lasted sixteen days longer and its course was very irregular. The pulse always remained slow. The spleen could never be palpated, and roseolar spots never appeared. The diarrhea lasted for three days, and the stools never contained blood.

The analysis of the urine was negative. Except during the first four days, the patient did not complain of headache or of any serious subjective symptom.

Treatment consisted in the exhibition of the usual intestinal antiseptics and in keeping the patient on liquid diet. From the stools an organism was isolated which clotted milk, slowly produced acidity in glucose, but not in lactose (reading taken on the seventh day). I called the bacillus *B. ceylonensis* A. It is interesting to note that the bacillus became capable later on of producing acidity in a number of sugars, and occasionally it may produce slight acidity in lactose after two to three weeks' incubation.

### CONCLUSIONS

(1) There are several clinical conditions in which organisms of the *metadysentery group* (*Lankoides-Dysenteroides* group) have been found. These conditions may be acute, sub-acute, or chronic. There may be dysenteric diarrhea or there may be simple diarrhea. In certain cases fever may be present and may be a prominent symptom, so much so, that

some form of enteric or parenteric may be suspected.

In this paper I have called attention to a chronic type of colitis characterized by recurrent attacks of diarrhea, generally simple diarrhea, but occasionally dysenteric for brief periods of time. Between the attacks the symptoms are somewhat indefinite and obscure. The patient feels tired, disinclined for work, nervous, and often complains of slight abdominal discomfort and flatulency. The symptoms are so indefinite that very different diagnoses are made: intestinal intoxication, intestinal subinfection, mucous colitis, abdominal neurasthenia, not rarely atypical appendicitis is suspected and an operation is performed.

(2) The metadysentery bacilli are intestinal bacilli similar to the dysentery bacilli, Shiga and Flexner, with regard to certain characters, viz., they do not produce gas in any sugar, they differ, however, from them as they either clot milk and produce acidity in lactose, or they clot milk without producing distinct acidity in lactose, or they produce acidity in lactose without clotting milk. Some species of the so-called metadysentery bacilli group (*Lankoides-Dysenteroides* group) are pathogenic, others probably are not. The two principal species I found in 1905 and published in 1907 and 1908, viz., *B. ceylonensis* B and *B. ceylonensis* A are, in all probability, pathogenic, and so is the *Bacillus metadysentericus* described by me. In the chronic conditions I have discussed, the blood of the patient generally contains a large amount of agglutinins for the variety of metadysentery bacillus isolated from the patient's stools, as

well as the same variety isolated from other patients with the same symptoms. In one of the recent cases (Case IV) three varieties of *Lankoides* were isolated from the stools—two (*B. ceylonensis* B and *B. ceylonensis* A) were agglutinated equally well by the patient's blood, and the agglutinins were specific, the third variety, a strain of *B. madampensis*, was not agglutinated, and was probably

non-pathogenic. This case was probably one of mixed infection caused by a strain of *B. ceylonensis* B + *B. ceylonensis* A of the metadysentery group.

I shall be pleased to supply workers interested in the subject with cultures of *B. ceylonensis* B, *B. ceylonensis* A, and certain strains of *B. metadysentericus*.

My thanks are due to Sir William Simpson for having carried out the animal inoculations in England.

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# Some Observations of Intestinal Amebiasis Due to Infection with *Entamoeba histolytica*\*

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THAT manifestation of intestinal ulceration due to infection with *E. histolytica* and known as amebic dysentery has been fully described with reference to its etiology, pathology, symptomatology and diagnosis. The dysentery itself may be due to a generalized ulceration of the entire large bowel with consequent colitis, or the ulcers may be confined to the sigmoid and rectum, and dysentery may follow this localized irritation.

For some years past it has also been known that quite severe and extensive amebic ulceration of the cecum, or the flexures, or other individual parts of the large bowel may occur without dysentery, or the lesions may be only a few ulcers, localized or distributed. In such cases there may be occasionally a bloody stool, but more often diarrhea alternating with constipation, and the symptomatology is varied in the extreme, so much so that the diagnosis cannot be made except by the finding of the specific agent, *E. histolytica*.

The many phases of the life cycle of this parasite will later be referred to briefly.

I will say at present only that in the small precystic and cyst-forming stages *E. histolytica* is difficult to find, and in fresh preparations from the stools, may easily be confused with similar phases of *E. coli*, *Endo nana*, and *Iodamoeba butschlii*, all three of which are frequently seen in the examination of the stools, and especially in sub-tropical and tropical countries. Nearly twenty years of work on this subject has convinced me, and, I may add, others better qualified than myself, that the correct diagnosis in fresh material of intestinal amebiasis not associated with dysentery, and the proper identification of the four species of amebae commonly found in the stools, is a task requiring long and special training, and is not to be entrusted, as it so often is, to the ordinary worker in the laboratory or the inexperienced technician.

The milder cases of intestinal amebiasis rarely come to autopsy except when complications such as liver abscess or perforation occur, or when death results from accident or some intercurrent disease or infection. Although the association between amebic abscess of the liver and dysentery has been notorious for many years, and indeed autopsy records show that

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when death follows untreated generalized intestinal ulceration due to *histolytica* infection there is abscess of the liver in over 50% of such cases, there are many reports of abscess of the liver on record without history of dysentery, and at autopsy the pathologist finds only a few scattered lesions, perhaps in the cecum, perhaps elsewhere in the large bowel

These are cases of amebiasis without dysentery, and the lesions, when uncomplicated by dysentery, may persist for years with few and intermittent symptoms. The pathologist, however, as far as I have been able to ascertain, has until very recently confined his researches to the gross and microscopic study of the larger lesions themselves and it has not occurred to him that there may exist quite extensive damage to the mucous membrane of the large intestine that is not readily visible macroscopically, or at least only after very careful inspection. Such a condition has been suspected by several workers, particularly, Dobell, Boeck, Wenyon and Craig, and although it has been found as a very early condition in the cat, it has only recently been demonstrated in man. I shall endeavour briefly to indicate the importance of this conception of amebiasis without dysentery.

In the stools of many apparently healthy and normal persons, sometimes with a history of previous dysentery or diarrhea, less frequently in those who have never had intestinal troubles, enormous numbers of the small *vegetative*, *precystic* and *cystic* forms of *histolytica* are found, quite as numerous as the larger vegetative

forms found in acute dysentery. And it is not at all unusual to find the parasite persisting in quantity under these conditions. It is well known that these very small forms measuring from six to ten micra are derived from the large vegetative forms living higher in the bowel, and represent that phase of the life cycle preparatory to encystment.

Now, some authorities, among them those above mentioned, have held that *histolytica* is always a true parasite of the human tissues, and that it must invade these in order to live. But if the enormous number of the small generations found at times in the stools of apparently normal persons actually represent tissue invasion higher in the bowel, such invasion would certainly result in severe ulceration with corresponding symptoms, and this does not inevitably occur. To explain this discrepancy it has been suggested that the invasion is confined only to the mucosa, and that the lesions heal readily, so that a continuous process of invasion and healing with complete restoration of the mucous membrane is taking place. These authorities do not agree that the parasite can live normally in the lumen of the bowel, and invade the tissue only at intervals, a hypothesis that would correspond to observed facts. They also maintain that the large number of active vegetative forms found in acute dysentery do not live and multiply in the lumen of the bowel, but generate in the tissues, and are thrown into the lumen by ruptures of the abscesses and discharges from the ulcers in the wall of the large intestine.

On the other hand there are those, among whom at present I am found, who hold that *histolytica* can live normally in the lumen of the upper part of the large bowel, and invades the tissues only under certain conditions, such as those which tend to irritate the mucosa, or when resistance is lowered

We base our opinion on the grounds that the number of parasites frequently encountered, in mild amebiasis as well as in acute dysentery, is out of all proportion to that found in sections of the intestinal wall in either case. Also, the well known tendency of a mild *amebiasis* to pass quickly into acute dysentery following dietary indiscretions or lowered resistance due to intercurrent disease, is evidence that something besides a latent tissue invasion has awakened a dormant infection into activity. It is only very recently, as I shall explain later, that proof has been obtained to show that large sections of the wall of the large intestine can be invaded without macroscopic lesions, and here no evidence of healing has been found, but rather a progressive damage.

Whichever hypothesis may be correct, there is one certain fact common to both, and concerning which practically all authorities are in agreement, and that is, whether it is always a tissue parasite, or whether it can live harmlessly for long intervals in the lumen of the bowel, *histolytica* is invariably an enemy of its host, actively or potentially, and should be treated as such whenever and wherever found.

Another important and frequently

overlooked factor in *histolytica* infection is the relative immunity of the human host. It is indeed fortunate that this is true, otherwise the ulceration would go on to perforation, and most of these infections would be followed shortly by a fatal peritonitis. The muscle layers of the large bowel offer a very considerable resistance to the passage of the amebae. One sees frequently large ulcers with few or not any amebae at the edges, and in many instances the damage is out of all proportion to the number of amebae present. So true is this that many believe a secondary bacterial infection from the lumen of the bowel is as responsible as the *amebae* themselves, and frequently there is no correlation between the number of *amebae* present and the amount of the damage, especially in *amebic* abscesses of the liver, lung, brain and spleen.

This fact may offer a clue to the successful treatment of *amebic* infection. If the lesions in the wall of the large bowel can be made to heal perhaps the *amebae* in the tissues will die, and this can be demonstrated in pathological sections. Nests of *amebae* in the tissues of the large intestine are invariably associated with abscess or ulcer formation communicating with the lumen of the bowel, although these nests may lie outside of the actual ulcerative process itself.

Conversely it may be said that if the amebae in the lumen of the bowel are removed, and re-infection prevented, the tissues will take care of their own amebae.

The usual description of an *amebic* ulcer is that it is flask or crater-shaped, pointing into the lumen of the



bowel, with its edges undermining the mucosa, and at times penetrating the muscle coats and even the serosa. According to Dr H C Clark, when the external muscle coat has been for the most part destroyed, the intestinal bacteria can pass through the serosa, and bring about a localized or general peritonitis. This process is often accompanied by a considerable hypertrophy of the wall, especially of the submucosa, and if the ulcer is advanced, by the formation of adhesions and bands.

The amebae are said to gain entrance through the crypts of Lieberkühn, from the bases of which they wander into the submucosa, and pass out radially in that tissue, the end result being the flask-shaped or crater ulcer just described.

This description is essentially correct as far as it goes, but it is not sufficiently inclusive. The amebae not only penetrate the lumina of the gland cells and the basement membrane, but not infrequently there is a direct invasion of the interstitial tissue as well. The result of this is a lysis and destruction of the mucosa, sometimes over large areas, without typical ulcer formation and without much invasion and destruction of the sub-mucosa. Dr Lawrence Getz, pathologist to the Santo Tomas Hospital in Panama, has demonstrated this process over six inches or more of the mucosa, unaccompanied by ulcer formation or destruction of the sub-mucosa. He has also found the very earliest type of lesion, so rarely that it might be thought merely a post-mortem change, were it not for the amebae found in the tissues.

Again, there may be an almost complete destruction of the mucosa, over large spaces, without ulceration and with very little invasion of the sub-mucosa. Such damage cannot fail to give rise to symptoms, and it is pathology of this type, with a few ulcers here and there, that is responsible for the clinical manifestations of amebiasis without dysentery.

Notwithstanding the careful studies of recent years, the exact mechanism by which *histolytica* produces tissue destruction is still undetermined. The earliest form of damage is very similar to that produced by chemical agents, a true lysis of the cells, without a reaction accompanied by round cell and *leukocytic* infiltration, a phenomenon that occurs later, and it may be due partly to bacterial invasion. But in all probability the amebae secrete a ferment that has a true *lytic* action against the tissue cells, and this is especially true in the so-called sterile abscesses of the liver and brain, where there is great tissue destruction without secondary bacterial invasion. But even in very early lesions without secondary bacterial infection and round cell infiltration, the damage is often out of proportion to the number of amebae present, and if the *lytic* action of the ferment be so powerful here, one might look to see this action continued later. It does not appear that gland cells are more susceptible than interstitial tissue, since in the latter, and especially between the glands themselves, areas of necrosis with few amebae are constantly found.

Very early there is also a marked congestion and at times a thrombosis of the terminal vessels of the circulatory

system, especially of the *capillaries* and the very small radicles of the *venous portal system*. This has been explained by stating that in the crater- or flask-shaped ulcers there is a stasis of the blood supply due to pressure and round cell infiltration.

But this congestion accompanies the very earliest lesions also, long before any mechanical factor can possibly be concerned, or any reaction due to secondary bacterial infection has taken place. It is a striking and constant phenomenon and suggests that even prior to invasion of the tissue by the amebae, these have brought about some irritation at the surface of the mucosa which results in this reaction. In its turn this brings up the thought that it is possible for *histolytica* to remain latent in large numbers in the lumen of the bowel, but when the occasion arises, for reasons as yet unknown to us, they begin to secrete a ferment irritative to the mucosa, and armed with this weapon of offense, hitherto unused, they begin their invasion.

I offer this suggestion solely for what it is worth. In truth there is so much about the mechanism of *histolytica* infection which is at present hidden from us, and it is so difficult to reconcile or to correlate the known facts and recent findings with any hypothesis, that I feel sure we must work for a long time yet, before we can postulate a definite and satisfactory conclusion.

It is not possible within the limits of this paper to discuss all the factors in amebiasis. If we have a definite knowledge of the essential facts of the pathology it is possible to induce

from these most of the symptomatology. I shall merely state that this is variable in the extreme. Intestinal amebiasis can simulate, directly or reflexly, practically every known gastrointestinal disease, from simple indigestion, with flatulence and occasional colic, to obstruction and cancer. I have several times seen amebic infiltration of the cecum and transverse colon mistaken for cancer, and with very good reason. Amebic typhilitis and non-amebic chronic appendicitis resemble each other so closely that the diagnosis often cannot be made until operation, and even here the two will frequently be associated.

With respect to diagnosis, it is my own opinion that except in cases of acute or subacute dysentery where the large, active, vegetative form is readily demonstrated, the findings in the fresh stools should be checked with permanent preparations. This is because in other types of amebiasis *histolytica* appears in the stools for the most part in the small vegetative or precystic stage, and here, in fresh preparations, it is very easily confused with *nana*, *butschlii*, and even with *coli*. It is true that a qualified expert working with absolutely fresh material, may be able to distinguish between these four species in the examination of fresh material. But such experts are few and far between, and are not often found in the practice of medicine or in attached laboratories.

Dobell well intimates that if the diagnosis cannot be made correctly, it should not be made at all, and since the treatment at best is tedious for patient as well as physician, a correct determination is of highest import-

ance This determination can be made with a very high degree of probability in the wet fixed or permanent preparations, by anyone capable of reliable clinical laboratory work In fresh material it cannot be made at all except by those with long and special training, and thoroughly familiar with the elements of microscopy Yet in more than one medical center untrained technicians are finding hystolytica in a high percentage of fresh

stool examinations, and clinicians are attributing a vast variety of *infirmities* from Hodgins' disease to chronic arthritis, to infestation with this parasite

Some of such errors in diagnosis, which I have encountered recently, I would not have believed possible, had I not seen them myself, to borrow a term of that eminent authority Prof Clifford Dobell

## Treatment of Endamebiasis\*

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THE introduction of ipecac and its derivations of various emetin compounds was thought to be the solution of a difficult therapeutic problem. With the passage of time ipecac and emetin have proved to be efficient in controlling the symptoms of acute amebiasis but they have proved a disappointment in a large group of cases with regard to eradicating the parasite. In the last few years it has been realized that treatment must be carried out along broader lines, and hence, many new preparations have been added.

Willner has recently reviewed his results with the use of yatren, stovarsol and auremetin. His cases were traced for from three to six months after treatment and from three to six stool examinations were made. The results were good in 90 per cent of eighty-eight cases in which yatren was used, in 90 per cent of thirty-seven cases in which stovarsol was used, and in 92 per cent of forty cases in which stovarsol and auremetin were used. Auremetin is the hydrogen periodide of emetin in combination with the dye

auramine, a drug introduced by Martindale and first used clinically by his associate, Willmore. The drug contains 28 per cent emetin and is administered in four one-grain doses by mouth on alternate days for a week. On the intervening days stovarsol is given. I have used auremetin in too few cases to evaluate it. Nausea and usually vomiting have been produced by the doses recommended so far and I have had to decrease it to 2 grains daily. Emetin is of immense value. It has been shown that if it is used alone a large percentage of cases relapse (1, 17) but the combination of an organic arsenical compound and emetin seems to be the best therapeutic measure. If auremetin should prove to be as useful as now seems probable, the hypodermic syringe may be dispensed with and all medication given by mouth, except in acute cases in which emetin administered hypodermically will still remain the most effective means of controlling the disease rapidly.

In an endeavor to evaluate the therapeutic results of some of these drugs the work during the last three years in the Mayo Clinic has been reviewed. Sixty-three cases of an earlier report (2) on the use of stovarsol are

\*Abridgment of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine, 1928

included, as additional data on many of these have been obtained

It is impossible to trace all patients treated in the clinic. Many patients begin treatment and continue under the supervision of their home physicians. Less than half of the patients treated here have been observed long enough to be included in this report. This study, therefore, is based on the data obtained from a group of 178 cases from which enough data are available to give some idea of the therapeutic efficiency of the treatment employed.

As a basis for efficiency of treatment the eradication of the parasite is held paramount. It is important to remember that the patient is more concerned with the subjective results than with the laboratory observation, in nearly all cases in which ameba is a cause of the trouble the patients respond promptly to treatment and most of them are soon restored to a state of normal efficiency. I have found that when *Endamoeba histolytica* is present and is a factor in the complaint, treatment of even a few days will prove this association of organism and complaints and yet the treatment may seem to have eradicated the parasite while the symptoms persist. This applies particularly to carriers, and thus any statements as to benefiting various ailments by treating the ameba must be guarded. Treatment is indicated from the public health standpoint and to protect the carrier from possible diarrhea following an acute illness, operation or from an abscess of the liver. If the attacks of diarrhea are steady or intermittent,

the prospects of relieving the condition are more definite. Here, again, there are exceptions to the rule, such as the possible influence of achlorhydria, or indeterminate diarrhea which bears some resemblance to sprue or pellagra.

It is not my intention to discuss incidence or diagnosis, but I shall again call attention to the value of making stool examinations for three successive days at least. In 112 cases (63 per cent) the ameba was identified in the first stool, in forty-four (24 per cent) it was identified in the second stool and in eighteen (10 per cent) in the third. Hence in 97.7 per cent of this series the ameba was recognized by three examinations. The remaining cases were identified by making smears from rectal ulcerations or from the pus of a draining abscess of the liver.

#### TYPES OF TREATMENT

Stovarsol (acetylaminohydroxynylarsenic acid) was first used in the treatment of endamebiasis by Marchoux in 1924. Since his first favorable report its use has extended to all countries. The original suggestion of giving the drug in 0.75 gm doses daily for a week has been changed to the same dosage daily for four or five days. Intolerance to the drug has been reported frequently, the milder reactions of toxic erythema did not cause undue concern but a number of cases of exfoliative dermatitis occurred. Two deaths have been reported (11, 19).

When the drug was first used in the Mayo Clinic (March 1925) the dosage was 0.75 gm daily for seven days but was gradually reduced until

it was given for four days. The immediate as well as the later results seemed to be as effective with the shorter course. If there was no intolerance, two or three more courses were given with an interval of ten days between courses.

In discussing results the expression "seem to be cured" will be used, the word cure demands prolonged observation and repeated stool examinations which is possible in few instances. When the term, seem to be cured, is used it will imply a disappearance of symptoms and at least two or more negative stool examinations.

Of the 178 patients treated, 130 received stovarsol only, five received both emetin and stovarsol. Of the 135 patients, 109 (80 per cent) seemed to be cured, of the twenty-six patients who had recurrence twenty-four took stovarsol again without benefit and two seemed to be cured by additional stovarsol. In the group of twenty-four treparsol (formyl amide of meta-amino-para-oxyphenyl-arsenic acid) appeared to effect the cure of three and not of four, yatren (10do-oxybenzenpyridin - sulphonate) appeared to effect the cure of four and not of five, six patients were only

temporarily benefited from bismuth emetin iodide and emetin. In the group of recurrences the patient with abscess of the liver, who died, is included.

Treparsol (formyl amide of meta-amino-para-oxyphenyl-arsenic acid) was first suggested in the treatment of amebiasis by Flandin in 1924, but its use has not been extensive. Treparsol was used first in the clinic in February 1926. My attention was directed to it by the statement that it was eliminated more rapidly than stovarsol. Stovarsol was effective but it was desirable to minimize all risks incident to its use. The apparently slow elimination might be a factor in reactions or in the development of neuritis. In order to ascertain the degree of absorption and ratio of elimination of arsenic in the urine and feces, following treparsol by mouth, an investigation was undertaken in collaboration with Osterberg. This work is being continued, from the data already available certain facts seem to be established.

Six patients (Table I) received a course of treparsol treatment which consisted of 0.75 gm daily for four days. This amount of treparsol con-

TABLE I  
SUMMARY OF RESULTS FROM ARSENIC

ARSENIC ELIMINATED			RATIO OF ARSENIC IN URINE TO ARSENIC IN THE FECES	COMMENT
URINE	MG FECES	TOTAL		
192	595	787	1/3	Treparsol chewed
184	546	730	1/3	Treparsol chewed
133	815	948	1/6	Treparsol chewed
45	741	786	1/16	Treparsol swallowed
70	645	715	1/9	Treparsol swallowed
125	1005	1130	1/8	Treparsol swallowed

tains approximately 800 mg of arsenic. The daily collection of urine and feces was begun at the onset of the treatment and continued for seven days. The arsenic estimations were made after the electrolytic Gutzzeit method, as described by Osterberg. Prior to the adoption of this method the estimations had been made in five cases according to the ordinary Gutzzeit method in which there is a preliminary oxidation of organic matter by alkaline fusion or by potassium chlorate. A quantitative recovery of arsenic in biologic materials was not obtained by this method.

The results of the estimations by the electrolytic method show that the major portion of the arsenic is eliminated in the feces. When the treparsol tablets were swallowed, the ratio of arsenic in the urine to that in the feces varied from 1:8 to 1:16. If the tablets were chewed thoroughly, the dispersion of the arsenic was greater and the ratio of arsenic in the urine to that in the feces was 1:3 or 1:6.

The manner in which the drug becomes effective is not known. Reports summarized by Stokes indicate that the ratio of elimination of arsenic in urine and feces is comparable to the results with treparsol in the Mayo Clinic. He further showed that the chief storage depots for arsenic are in the liver, spleen, and intestinal tract. The amount of arsenic in the walls of the intestine is evenly distributed according to the experimental work of Clausen and Jeans. It is not known whether or not there is constant absorption of arsenic by the entire intestine but it would seem that the

effectiveness of treparsol may depend more on the amount of arsenic in the wall of the bowel than on the amount in the content of the bowel. The disease process in endamebiasis is in the wall of the bowel and it would appear desirable to use a drug which obtains access to the walls of the colon either by direct absorption or by virtue of its presence there as a result of arsenic in the blood stream. It would seem that the ameba would be more affected by the drug in the mucosa and submucosa than by its direct action as it passes along in the fecal current. There must be an individual variation in the absorption of arsenic as is shown by the two cases in which only 45 mg and 70 mg were excreted in the urine. It is possible that one of the explanations for the reaction of the skin to the drug may be found in the fact that certain persons may absorb the drug more rapidly or eliminate it more slowly than in the cases in which there is no difficulty. Opportunity has not been afforded to study this question since in the cases in which elimination studies were made the patient did not suffer from reaction.

In each of the six cases studied, approximately all of the arsenic was eliminated by the end of the seventh day after treatment was begun. The variations in the total output of arsenic, compared to the intake of approximately 800 mg, merely illustrate the almost unavoidable discrepancy in biologic materials. Particles of the tablet may or may not be included in an estimation of the drug in feces and this will cause an apparent discrepancy. The estimation of

the drug in the urine should be accurate although there is the possibility that one or more specimens may be lost during the week. The results are sufficiently accurate to warrant the conclusion that approximately all of the arsenic is eliminated three days after the completion of a course of twelve tablets and if four or five additional days are permitted to elapse before the institution of a second course, the chances of an accumulative effect are slight. Treparsol was given in 0.75 gm doses for five days and shortly decreased to four days because of experience gained in its use. Thirty-nine patients were first treated with treparsol, thirty-eight of whom seemed to be cured. Eleven of these were given 4 to 14 grams of emetin in addition to the treparsol and none had a recurrence. Seven patients who had had stovarsol were given treparsol and three of these seemed to be cured. Hence forty-six patients received treparsol either at the onset of treatment or following recurrence after the use of stovarsol. Of these forty-six patients five (11 per cent) had recurrences and forty-one (89 per cent) seemed to be cured. This is comparable to the 80 per cent result with stovarsol as the treparsol series is smaller and the drug has not been used as long as stovarsol. Reactions have occurred, similar to those with stovarsol. One death from its use has been reported.

Only a few patients who suffered from recurrence following stovarsol or treparsol received more than temporary benefit by continuing the drug. There is some risk in persevering with either arsenic or emetin indefin-

itely and it is advisable to change to other drugs or different combinations. Certain patients who have been treated with only one or two drugs have continued to suffer from diarrhea. Changing drugs has been successful in several instances.

The group of twenty cases (Table 2) shows what may be accomplished by changing to a different drug or to a combination of drugs. Although these patients may not be actually cured, the results have been encouraging, particularly as all patients had had more or less persistent treatment which was of only temporary benefit. In one case the patient had been treated intensively with arsphenamine, emetin, bismuth emetin iodide and so forth, but diarrhea persisted. In fact the disease had persisted long enough (twenty years) to produce contracture of the rectum, a complication that may develop in chronic cases, and emphasized the foothold the ameba had gained. The patient was given 20 gm of treparsol in divided courses, a year later diarrhea had stopped and examination of four stools was negative. Three months later he returned to have an operation for anal fistula, there was no recurrence.

The intestinal tract as a depot for arsenic may be an explanation for failure to obtain permanent benefit from the use of stovarsol or treparsol. Strains of ameba may become tolerant to the prolonged presence of the arsenic in the wall of the intestine. This theory has been suggested by various syphilographers in the case of resistant syphilis when it is thought that certain strains of the *Treponema pallidum* may become tolerant to the drug.



TABLE II  
VALUE OF VARYING TREATMENT IN RECURRENT CASES

CASE	DURATION OF DIARRHEA, YEARS	FORMER TREATMENT	PRESENT TREATMENT	COMMENT
22	1 5	Stovarsol	Yatren and stovarsol	Seemed cured, four negative stools
23	1 5	Stovarsol and emetin course	Yatren	Seemed cured, four negative stools
26	30	Stovarsol and three courses emetin	Treparsol, emetin and yatren	Seemed cured, reported five months later no diarrhea
30	4	Emetin course, bismuth, emetin iodide	Treparsol	Seemed cured, three negative stools, reported well three months later
31	20	Emetin, arsphenamine, ipecac, bismuth and bismuth emetin iodide	Treparsol	Seemed cured, six negative stools one year later, four negative stools and no diarrhea
39	5	Emetin	Stovarsol	Seemed cured, two stools negative six months later
52	0 16	Stovarsol	Yatren	Seemed cured, three stools negative three months later, reported well eight months later
64	1	Emetin course	Stovarsol	Seemed cured, one stool negative one year later
70	25	Emetin	Treparsol	Seemed cured, two negative stools
76	9	Emetin and Stovarsol	Yatren	Seemed cured, three negative stools, reported well two months later
90	1	Stovarsol, trep- arsol, emetin and yatren	Treparsol and Emetin	Seemed cured, three negative stools
92	6	Emetin course	Treparsol and Emetin	Seemed cured, four negative stools
94	13	Emetin course	Stovarsol	Seemed cured, three negative stools, four months later re- ported no more diarrhea
98	4	Emetin course	Stovarsol	Seemed cured, three negative stools

TABLE II (Continued)  
VALUE OF VARYING TREATMENT IN RECURRENT CASES

CASE	DURATION OF DIARRHEA, YEARS	FORMER TREATMENT	PRESENT TREATMENT	COMMENT
111	10	Emetin course	Treparsol and yatren	Seemed cured, three negative stools, one year later three negative stools and no diarrhea
148	0.5	Treparsol	Yatren	Seemed cured, three negative stools, six month later reported no diarrhea
154	1.3	Stovarsol	Yatren	Seemed cured, three negative stools, three months later reported no diarrhea
155	1	Emetin	Yatren	Seemed cured, three negative stools, four months later two negative stools and no diarrhea
158	4	Emetin and stovarsol	Yatren	Seemed cured, two negative stools, three months later no diarrhea
160	10	Emetin	Treparsol	Seemed cured, three negative stools

Another possibility is suggested by the observation that certain persons may take stovarsol for long periods without apparent injury, and thus may merely keep the activity of the ameba at a point to enable them to continue work. There seems to be a state of "armed neutrality" whereby the parasite and the host continue to progress the former in spite of the arsenic and the latter in spite of the ameba as long as arsenic is taken. Two patients have consumed what would seem to be an enormous amount of arsenic and yet have not been relieved, nor has any demonstrable injury from the arsenic resulted. In one of these the patient has recently received yatren and seems to be cured. The other patient has tried emetin,

and the arsenical compounds but is still distressed, in order to continue work he resorts to frequent courses of stovarsol. One is inclined to speculate on the possibility of injury later, particularly the change that may ultimately take place in the liver. The same may be true of emetin. It has seemed to me that emetin-fast strains of ameba develop in certain persistent cases of diarrhea (1). Dale and Dobell have suggested that the actual amount of emetin in the blood stream is much less than the amount required to destroy the ameba experimentally. From this they consider that there may be a change in the reaction of the host as a result of prolonged administration of emetin and that this, rather than a change of

ameba to an emetin-fast organism, is the explanation

From a practical standpoint, the present conclusion is that variation in treatment in recurrent cases is indicated. Ipecac, various emetin compounds, and organic arsenical compounds for both oral and intravenous administration and iodine in the form of yatren are available as remedies. Other remedies, although less effective as a rule, are Chapparo amargoso, massive doses of bismuth subnitrate, irrigations of the colon with hot (42 to 44°C) solution of sodium chloride, kerosene, and so forth.

Because of increasing experience with treparsol and stovarsol and a certain number of recurrences it was thought that a combination of treparsol or stovarsol and emetin might prove more effective than either drug used alone. This regimen was carried out in eighteen cases. One of hepatic abscess need not be considered in evaluating the remainder of the group. This patient was practically moribund before treatment was instituted. In the remaining seventeen cases there are two known recurrences, and six patients who were well from three to twelve months after completing treatment. At present, treatment is begun with both emetin and treparsol unless the patient has previously been given either or both of the drugs. In such instances yatren is employed at the beginning of treatment.

Iodo-oxybenzenpyridin - sulphonate (anayodin, yatren) was first used in the treatment of amebiasis by Menk in 1922. Its use spread first to the Orient and Far East, few reports

are available of its efficiency in this country. Turner and Jones reported a group of eight cases in which yatren was used. Willner reported favorable results in seventy-nine of eighty-eight cases in China. In a review of the literature he found that from 66 to 92 per cent of patients were believed to be cured by yatren. It is given by mouth in 3 gm doses daily for a week and repeated after a week's interval for two or more such doses. Oral administration in conjunction with irrigations of the colon of 1 to 2 per cent yatren is recommended by many. The drug may increase the diarrhea so that the amount of the drug given daily must be decreased. Other untoward symptoms from its use have not been observed. Irrigation has not been used in The Mayo Clinic. Yatren was first used in April 1926 and has been given to eighteen patients in this series. Eleven of these seemed to be benefited while seven suffered further recurrences, the latter had had emetin, treparsol or stovarsol and usually bismuth emetin iodide. The same gamut of treatment was run by seven patients treated successfully. It is possible that better results might have been obtained by irrigations of yatren in conjunction with the oral administration.

The results in this small group indicate that yatren is valuable in the treatment. If it were used first, the percentage of favorable results might be as high as with arsenic, as Willner's article seems to indicate. For the present yatren is administered to patients who have had recurrences either in the clinic or elsewhere after taking arsenic or emetin. Emetin and

arsenic have failed in such cases and yatren is used for two main reasons first, to give either the host or the parasite a change from previous treatment, and second, to minimize the possibility of the accumulation of arsenic or emetin

#### ADDITIONAL DATA ON THE RESULTS OF TREATMENT

Data from reëxamination of patients after a period of three months are shown in Table 3. Fifty-eight of

recurrence was not recorded. The case of abscess of the liver need not be considered in estimating the time of recurrence. Of the remaining twenty-four cases there was recurrence in eighteen, or almost 75 per cent, within eight weeks, in three cases there was recurrence within four months, and in two cases within six and eight months respectively.

MacAdam found that thirteen of eighteen relapses occurred within four weeks and Gordon that 65 per cent appeared within two months.

TABLE III  
CASES IN WHICH CURE HAD APPARENTLY BEEN EFFECTED

TIME AFTER TREATMENT, MONTHS	TWO TO TEN STOOLS NEGATIVE, CLINICALLY WELL	STOOLS NOT EXAMINED, CLINICALLY WELL	TOTAL
3	11	7	18
6	19	5	24
12	9	2	11
12+	4	1	5

the patients seemed to be cured from three to many months after completion of treatment. If more than six months had elapsed without symptoms and the stools were negative, and if amebic dysentery again appeared, the possibility of reinfection is as strong as that of recurrence. It is better, however, to consider such conditions as recurrences for it is difficult to prove reinfection. The majority of the twenty-seven patients known to have recurrence were observed to have symptoms soon after cessation of treatment. There were a few exceptions and again there is the temptation to seek the explanation by reinfection rather than by recurrence.

In two instances the date of recur-

Hence there are available subsequent data concerning fifty-eight patients apparently cured and concerning twenty-seven with recurrence. Some of the remaining ninety-three patients may have had recurrences but one derives consolation from the fact that failures are usually reported.

#### COMPLICATIONS OF TREATMENT

Stovarsol or treparsol was used in 174 cases. In six (4.4 per cent) of 136 cases in which stovarsol was given, toxic erythema developed from the fifth to the tenth day. The dosages ranged from 3.75 to 5.25 gm. In three (6.5 per cent) of forty-six cases in which from 3 to 9 gm. of

treparsol had been given, toxic erythema developed. In two cases it appeared on the fourth and fifth day, while in one it did not occur until after the completion of the second course of the drug. In one case in which enough of a skin reaction developed to be considered a mild manifestation of exfoliative dermatitis, treparsol was used.

In some of the cases in which erythema developed an antecedent acute upper respiratory infection was thought to have some possible relationship to the development of the skin reaction. Morgan suggested that arsenic may produce enough irritation of the mucous membranes to simulate coryza. In either event, it is safer to withhold arsenic temporarily if the patient has a cold or tonsillitis. Also, if the slightest suspicion of skin irritability develops, or if any peculiar symptoms are mentioned by the patient, it is well to withhold the drug until all doubt is gone.

In the nine cases of toxic erythema, recovery was complete within a week. The patients were kept in bed as long as fever persisted. Fluids were increased and a moderate amount of alkalis given by mouth. Three patients received, intravenously, sodium thio-sulphate, while this probably increased the rate of elimination of arsenic, it did not exert any outward effect on the dermatitis or shorten the illness. The patients were advised against the further use of arsenic but were told to rely on an emetin preparation, yatren, bismuth, and so forth. The advice was disregarded by one patient who took both emetin and stovarsol later. Mild peripheral neuritis developed al-

though a skin reaction was not reported. In two other cases in which stovarsol was given peripheral neuritis developed. In one case 7.5 gm of stovarsol had been given in divided courses while in the other several courses with a total of at least 22.5 gm of the drug given. In both cases arsenic was present in the urine many weeks after stovarsol had been taken. The slow elimination of the arsenic should explain the neuritis and emphasize caution in the amount and repetition of courses of the drug. Individual susceptibility is significant in these complications as in all types of drug reaction. Jaundice as a complication in the use of stovarsol or treparsol has not occurred in any of my cases.

#### RESULTS OF TREATMENT IN VARIOUS TYPES OF ENDAMEBIASIS

In a previous paper (1) I referred to amebic cases in three main groups. The division is somewhat arbitrary but serves as a working basis for clinical study. It further serves to help settle the question as to the results of treatment in the different types of cases in which the ameba may occur. Group 1 includes cases in which active symptoms of dysentery or hepatic abscess were manifested at the time of admission. Sixty of the 178 cases were in this group. Group 2 consists of 102 cases in which the chief complaint, or one of the complaints was intermittent attacks of diarrhea, sometimes alternating with constipation. Although the history of attacks of diarrhea suggests search for ameba, its presence need not be the cause of the abdominal complaints, a therapeutic test may be necessary to prove any

relationship Group 3 shows sixteen cases in which the ameba was found without recorded history of dysentery. Three cases were of persons who seemed to be perfectly well and in whom the ameba was found incidentally as a result of stool examination. In three cases the patients were suffering from dermatitis and stools were examined for this reason. Eleven patients had normal or constipated stools, search for ameba was made because of indefinite abdominal complaints.

*Group 1*—In this group of sixty cases proctoscopic examination revealed amebic proctitis in twenty and one of an indeterminate type of proctitis. In eight cases free hydrochloric acid was absent in the gastric contents after a test meal, in three of this group, bowel symptoms persisted after eradication of the ameba, but were controlled by dilute hydrochloric acid. In two cases the patients had abscess of the liver. Fifty-six of the sixty patients seemed to be cured, they had had two or more negative stool examinations at the conclusion of the first course of treatment. Three patients manifested a satisfactory clinical response but stool tests showed persistence of the ameba. One patient suffering from abscess of the liver died. The other patient with abscess made an uneventful and speedy recovery. When heard from three months later he had continued to improve and apparently there was no reactivation of the disease in the liver. Fifty-nine patients were advised to carry out further treatment at home. In this group there are known to have been fourteen recurrences. It is significant

that ten of these fourteen patients had typical amebic ulcerations in the bowel, as determined by proctoscopic examination. One patient had an indeterminate type of proctitis which improved temporarily but recurred in four weeks. There was again improvement with the use of stovarsol and emetin. In the remaining three cases of recurrence there were no ulcerations of the rectal mucosa.

*Group 2*—In this group of 102 cases, there are two cases of idiopathic ulcerative colitis (not amebic colitis) in which the ameba was found to persist after a course of treatment. In three cases of ulcerative colitis, the ameba seemed to have been eradicated. In all these five cases anti-amebic treatment was of some value. The important diagnostic point, however, is the recognition of ulcerative colitis associated with actual amebic colitis or, what is more common, the mere coincidence of the ameba which may play little if any part in the activity of the colitis. It is necessary to treat the amebic infection and at the same time suitable measures should be directed toward the other disease. In some instances the patient must be observed until the effect of the treatment of the amebic condition can be determined, and then if the colitis persists other treatment may be employed. In the remaining ninety-seven cases, there were nine recurrences. In six amebic proctitis was present and in three proctoscopic examinations were negative. Again the high incidence of proctitis in recurrent cases is noted.

The cure of eighty-eight patients in this group may be more apparent than

actual although reports thus far are encouraging. It is possible that the patients were less severely infected, or the factor of individual resistance may determine the amount of trouble that will result. Particularly in the cases without amebic proctitis it seems reasonable to expect cure. One case, however, illustrates the difficulty that may arise in the consideration of some cases in this group. The patient complained of attacks of abdominal cramps of an indefinite type associated with loose to watery stools. Roentgenograms of the colon and proctoscopic examination were negative. In the examination of the stool, *Endamoeba histolytica* was identified. As the ameba was the only tangible objective observation, stovarsol was administered and at the conclusion of treatment three examinations of the stool were negative. There was no subjective benefit from the stovarsol and further treatment with stovarsol was advised. The patient was seen again four months later. The abdominal cramps were unchanged. *Endamoeba histolytica* was again identified in the stool. A course of emetin was given and later a course of yatren. Neither drug seemed to affect the distress. In view of the presence of the parasite at the second admission it might be thought that the persistence of the parasite was the reason for the continuation of symptoms. I believe that the ameba bore little if any relationship to the complaints. As I have stated, in cases in which the ameba is related to or is the cause of the complaint, treatment has seemed to evoke a prompt clinical response. Even in cases in which the parasite

presents at the conclusion of the first course of treatment or in which recurrence develops in even two or three weeks there is an immediate symptomatic response to specific treatment. On this basis the evidence does not seem sufficient to consider this patient's symptoms as due to ameba.

*Group 3*—Most of the cases in which the ameba is found occur in this group. Unless a survey is undertaken or routine stool examination made, only a few such patients will come under observation for treatment. Of the sixteen patients treated, the three who apparently were well were free of the ameba. Two of the three patients suffering from dermatitis were apparently benefited. The parasite was eradicated in all three. Arsenic has long been used in the treatment of various types of dermatitis. These patients received stovarsol or treparsol. It is probable that the arsenic exerted a nonspecific effect rather than that the parasites played any part in the lesions of the skin. In conjunction with the Section on Dermatology in The Mayo Clinic types of dermatosis were treated in which not only *Endamoeba histolytica* but other intestinal parasites were present. The clinical results were disappointing and failed to establish any direct etiologic relationship between intestinal parasites and dermatosis. Four of the ten remaining patients in this group considered themselves definitely benefited. Seven were not clinically benefited. In none of the ten cases could the parasite be found on repeated examinations. It is difficult to evaluate the results of eradicating the ameba in the four cases, as

the other factors of correcting dietary errors, constipation and reassurance that a serious disease was not present, all must be considered before too much significance is attributed to the ameba. In a previous report (3) twenty-two patients of Group 3 were treated. There was no definite clinical benefit as far as the complaint was concerned in any of them. Combining the two series of sixteen and twenty-two patients, it is difficult to accept any conclusion other than that the presence of ameba in the absence of a history of diarrhea is not likely to bear any relation to the patient's complaints. An exception must be made in certain cases of abscess of the liver in which there is no history of diarrhea. Thirty-eight cases are much too few from which to make final deductions, but each year continues to confirm this impression.

#### AMEBIC PROCTITIS

Attention has been directed in this and in previous reports (15, 19) to the fact that patients suffering from proctitis are more likely to suffer from recurrence.

In this group the five cases with ulcerative colitis and the two cases with an indeterminate type of proctitis are omitted. This is for the purpose of more clearly discussing the problem involved in this group of cases. There were forty-one cases in Groups 1 and 2, which showed typical amebic ulcers as determined by proctoscopic examination. In sixteen (39 per cent) of the forty-one cases there were recurrences. For more accurate comparison the five cases of ulcerative colitis and the two indeterminate cases

of proctitis are also deducted from the total number in Groups 1 and 2, which leaves 114 cases in which proctitis did not exist. Of this group of 114 there were seven (6 per cent) known recurrences.

Too much significance must not be attributed to the 94 per cent of cases without proctitis in which cure seemed to be effected. I believe that this percentage is high, but the important point is that the majority of the recurrences are in cases of proctitis. This strongly emphasizes the necessity of thorough treatment and long observation in such cases. In cases of amebic proctitis the infection must be from a more vigorous strain of ameba or else resistance of the host is lower than in the other cases.

The incidence of proctitis occurring in endamebiasis in the north temperate zone is probably more than from 6 to 10 per cent of the cases that have diarrhea due to the presence of the ameba. No significance can be attached to the forty-one cases (25 per cent) of the 162 cases in Groups 1 and 2 as an index of the incidence of proctitis as this is a selected group and represents only a part of the cases examined during a three-year period.

#### CONCLUSIONS

- 1 The organic arsenical compounds and yatren seem to be valuable additions to the treatment of endamebiasis.

- 2 At present, the most favorable results seem to be obtained from a combination of an arsenical compound and emetin. Auremetin by mouth may supplant emetin hypodermically except in very acute cases.



3 Simplification of treatment and an increase in efficiency are obtained by these methods

4 Treparsol and stovarsol are equally efficient but since treparsol is rapidly eliminated, it would seem to be preferable to stovarsol

5 Arsenic produces a small percentage of reactions Indiscriminate usage of the drug is not without risk

6 In cases with proctitis, recurrence is more probable than in those without gross ulcerative lesions.

7 Certain cases seem to be very resistant to treatment but persistence and variations in types of treatment should effect a cure in the majority of such cases

8 Much is yet to be desired in the treatment of the persistent and chronic phases of endamebiasis

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# Chronic Pancreatic Disorders, Diabetic and Non-Diabetic\*

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THE importance of the pancreas as an organ in the economy is best expressed in the fact that a continuous loss of pancreatic fluid is fatal and death occurs in a few days after the removal of the gland. Compared to this continued loss of gastric juice, its absence, and even removal of the stomach, or the continuous loss of or blocking of bile, or loss of duodenal secretion, are without lethal effect.

Up to and since the work of Opie (2) but little in the way of investigation has been done in disorders of the pancreas (other than such as pertains to the islands of Langerhans, diabetes and insulin). Considerable effort has been spent to devise tests for estimating the external secretion, all of them being of little value for clinical work. Interest in such tests was cogent because examination of the stools for fat, muscle fibre, undigested nuclei and carbohydrates, and the urine and blood tests, too often were negative in the positive cases, and always negative in moderate and minor grades of disorders of the gland.

The value of duodenal intubation

\*Read before the American College of Physicians, New Orleans Clinical Week, March 8, 1928

and the test (3) devised by me based upon its diastatic power has had application, and this with the new findings pertaining to the physiology of this enzyme (4) are the basis of this article. This test for pancreatic efficiency has now been studied for five years in practically fifteen hundred individual instances as well as in a considerable number of proven cases. The results of this large experience with the test now prove it to be a worthwhile method for clinical use, inexpensive and easily applicable for clinical purposes.\*\*

There exists a stern necessity for research work on disorders of the inter-related activities of the pyloric function, secretions of the biliary apparatus, duodenal mucosa and detail as to portal absorption, liver storage, food oxidation and eliminations. Largely because so little is known of these factors in digestion, in which the functions of the pancreas occupy an im-

\*\*Although the active principles of the thyroid and suprarenals are crystalline substances, insulin is either a colloid or intimately bound up with colloidal material. The same is true with the amylase (amylolysin) of the pancreas. It is interesting to observe that both of these active substances of the pancreas are recovered in this chemical form.

portant role, it is difficult to present clear pictures of clinical phenomena. Research work on the pancreas proves that this gland is as essential an organ in the body as the heart, liver, lungs and so forth, and like all essential organs has an independent function which continues at all hazards, and largely irrespective of emotional and often serious grades of disorders, however active they may be in depressing other secretions. Even with our lack of knowledge, and in spite of the dominance of function, disorders of external as well as internal secretions do occur, these apparently not always being due to organic diseases of the gland. It is only by assiduous studies in the future that these will be better known and classifiable in an entity sense. With the hope of stimulating further study and with no intention of being taken as definite, the following is submitted to serve as a classification. It must be remembered, as in chronic nephritis, that two or more states may co-exist.

*Hypopancreorrheic states, functional*

*Hypopancreorrheic states, consequent to infections of the biliary tract*

*Hypopancreorrheic states, organic, non-diabetic*

*Hypopancreorrheic states, organic, diabetic*

*Hypopancreorrheic states, malignant and granulomatous*

In 1917 Wardell stated—"No symptoms are pathognomonic of pancreatic disease, an assemblage of symptoms indicate the probability of its lesion." To this we may add the most useful procedure in the test proposed by me. With these, a knowledge of the

pathology of the pancreas and the biliary apparatus, and the means now at hand for diagnostic study of gastro-enteric conditions, quite accurate work on the pancreas is possible.

Of the signs and symptoms that play in some of these cases the following may be mentioned. *Asthenia*, weakness, loss of weight, tumor (palpable or observed by X-ray in defect in the duodenum), so-called intestinal indigestion, indefinite pain, pressure sensations and tenderness in the center of the abdomen, anorexia, cyanosis from marked to very slight and transitory states, vomiting, more or less acute disturbance in the abdomen closely simulating an attack of gall stones, colic or perforation, constipation, diarrhea and jaundice. To these may be added the sympathetic ocular or Loewe's test (which is not dependable), the uncommon signs of defects of external secretion in steatorrhea and azotorrhea (all of which are late symptoms and most often are not found in the positive case), and those defects of the internal secretion in glycosuria, lowered sugar tolerance and the Cammidge reaction (all of which are helpful in the diabetic types, but fall short of being clinically useful or dependable so far as the condition of the whole gland is concerned). Any of these and many others may be helpful as additional points in diagnosis, but none individually, or all collectively are commensurate in value to the test recently advanced.

*Hypopancreorrheic states, functional*. The function of the pancreas is very rarely depressed for emotional reasons. The emotion must be of the

depressive type (and as far as I know be due to grief) and it must be sustained for days before deficiency of the pancreas will occur. When it does occur it is only transitory, and even though the emotion be continued, the organ resumes its function.

A woman of 35 years was in an automobile accident in which her husband and their two children were killed, she being wounded and shocked. For days she was in deep grief, took practically no food and slept little. On the fifth day she became ill, vomited and was prostrated. On the sixth day the test showed but 4 units. Two weeks later there were 16 units, and in six more days there were 18 units.

It may be that in the average type of continued fear and anxiety no effect on the pancreas will occur. In the instances here in which the test was made it was always negative. As stated before, apparently the pancreas is resisting the psychic and the usual emotions that will so distinctly affect the stomach, colon and kidneys.

Late in adynamic diseases when severe weight reduction has taken place, such as in pulmonary tuberculosis, cancer, yellow fever and Hodgkin's disease, the pancreatic function is very apt to be low, probably because of the general debility. Low unit readings have been found in the diseases mentioned. On the other hand, in several extreme cases of typhoid fever, ulcerative colitis and amebiasis, the units have been ample. It is probable that in some diseases the external secretion of the gland would be affected, yet in many lethal diseases it may not be interfered with at all in the life of the patient.

It seems logical to believe that the pancreas may run low in function in

a reflex way. The instances in which this has been found most distinct are shortly after an attack of biliary colic from stones and in cardiac decompensation.

A woman of 42 years who had suffered from gall stones for years but had never had an attack of biliary colic was suddenly seized with one in which (because of the persistency of the pain—17 hours) an impacted stone with a hemorrhagic pancreatitis was suspected. She was not operated upon. On two examinations the units were but 2, and did not go above 4 until three days after all of the tenderness, nausea and anorexia had disappeared when the units were 10, and two weeks later 18, the latter two examinations being made on the tenth and fifteenth days after the colic had disappeared.

It is possible here that the low unit reading was due to some pancreatic depression of a transitory type. In all four cases of biliary colic that have been tested, three showed a low unit reading for a few days after the attack, and then became normal in one to three weeks time. There was one instance in which the units rose, but not to normal, subsequent to operation which proved an indurated pancreas.

Five cases of extreme degrees of cardiac decompensation were tested and all but one showed low unit readings with elevations taking place on improvement in the heart condition. The average cardiac case with mild degree of cardiac decompensation does not show a low unit reading, and it is possible that when a low unit reading occurs in the extreme case that it has a circulatory cause operating in the pancreatic blood vessels rendering the function of the gland deficient for the time being.

In the occasional case of arteriosclerosis seen, in which severe reduction in weight and strength has taken place, deficiency of pancreatic function should be suspected. In the diffuse form of this disorder and occasionally in the senile type, the vessels of the celiac axis may be markedly involved. When this is the case the pancreatic vessel is involved and thus the function of the gland will suffer. It is possible here that the loss of weight and vital exhaustion are due as much to this single item as any other. Four of such cases with units below 10 have been studied, three of which made substantial improvement in general health on frequent small meals and pancreatic feeding.

It is possible that the pressure of large pancreatic cysts may cause a deficiency of function. A case of small cyst was studied, the units being within normal range. Another case of small stones in the duct of Wirsung was observed, also with normal units. There now remains of this group a medley of cases which clinically, and because of deficient knowledge, can only be classed as functional, although it is probable that many of them are organic to some degree at least. In them various symptoms of digestive types and mainly intestinal in location are present. Among the symptoms correlated are loss of weight, anorexia, nausea, excessive intestinal gas, vague pains here and there in the abdomen, constipation, diarrhea and others. When pancreatic estimations are routinely made, whatever the other diagnoses made, or causes for the symptoms are believed to be, here and there a low pancreatic individual is met with

and one in whom dieting and pancreatic therapy are helpful. Occasionally one sees an individual in whom the diagnosis of biliary colic or even perforation is suspected because of the acuteness of onset and the intensity of the symptom of pain. Some of these are due to small isolated hemorrhages in the pancreas during which time the unit readings would be absent or low, the case recovering completely in a few days time.

A college boy 23 years of age was suddenly seized with an acute pain in the upper abdomen without contraction but with marked nausea and vomiting. He had no units in the test. It being deemed wise to open his abdomen for investigation, this was done thirty-two hours after the onset of the illness. Everything was negative except that his pancreas felt somewhat boggy. There were small hemorrhages discernible here and there along its course. The abdomen was closed without anything more being done and he made a smooth recovery. On the ninth day after the operation his units were 8 and on the twentieth day they were 14.

The above case, and two others of like kind that were not operated upon, suggest that there may occur very modified types of acute pancreatitis with slight hemorrhages which would throw the pancreas into abeyance of function for a short time, the condition recovering under simple medical treatment. Two instances of marked acute hemorrhagic pancreatitis that had been operated upon (one having a small pancreatic fistula that persisted) showed within six months after operation normal function of the gland.

*Hypopancrœrrheic states consequent to infections of the biliary tract.* The gall bladder is rich in lymphatic ducts

Some of these course to the liver, many of them empty in the glands about the bile ducts from which communication takes place into the pancreas and from thence to the lumbar glands. Infections and their toxemias from the gall bladder may be carried to the liver, bringing about congestion and fibrous formation in that organ, and from the ducts as well as the sac these often gain entrance into the head of the pancreas (a toxic lymphangitis), bringing about congestion, fibrous formation and even degeneration in the acinus cells, the latter sometimes extending into the islands of Langerhans. Enough anatomical, medical and surgical evidence is on hand to prove that the pancreas can and often does become affected from gall bladder conditions. Taking up the study of gall bladder disease from the standpoint of the activity of the pancreas, as to how often and to what extent it causes interference with the pancreas, and reversely studying gall bladder diagnoses from estimations of pancreatic activity some quite worth while new clinical data have now been collected.

In a series of gall bladder abnormalities verified by operation, the average figure is 61.5 units, and of those in which stiffening of the pancreas was noted  $2\frac{1}{2}$  units is recorded. Surgeons have reported pancreatic stiffening in from 5 to 20 per cent of gall bladder operations. The personal equation of surgeons and degree of care in the examination of gall bladder cases varies distinctly making statistics almost worthless. In my series, the pancreas was considered stiffened before operation in 67 per cent and negative in 33 per cent. Of these all who had

pancreatic hardening (usually of the head alone) showed low units, and in those in which it was negative the units were normal or above. In this series the Meltzer-Lyon method of examination was positive in 45 per cent and negative in 55 per cent. Added to these were the non-verified cases of cholecystic and duct disease in all of which the units were less than 10 with only 36 per cent having normal or above normal figures. In these, compared to the verified cases, strangely enough the Meltzer-Lyon was positive in 60 per cent and negative in 40 per cent. While the diagnosis might have been in error in some of the non-verified cases, positive Meltzer-Lyon tests were lower in those in which distinct pathology was unquestionable. On the basis of these findings the history, physical examination, cholecystography and icteric tests were employed for diagnosis, the Meltzer-Lyon test being discontinued and the pancreatic test employed to diagnose pancreatic stiffening. The latter was considered important to separate the surgical from the medical cases of cholecystic disease and to serve as a means of further study of the cholecystectomized individuals who returned with original symptoms and in whom adhesions and retained stones did not seem to answer as the cause.

In the year of 1925 one hundred instances of cholecystectomy done for stone and non-stone conditions studied after operation, showed fifty-one returns with symptoms, often the exact duplicate in intensity or in modified forms of those present before operation. Other than in those who had had attacks of biliary colic (in which

the post-operative result was almost perfect) the difference in the stone and non-stone cases was not marked in favor of either one from relief of symptoms. In 1926 and 1927 pancreatic efficiency was studied routinely. In all there were three hundred and ten cases of supposed gall bladder disease, and grouping the stone and non-stone cases together, sixty-two were operated upon, cholecystectomy being done. There were five cases in which a mistake in the provisional diagnosis was proven and two deaths. Of the fifty-five confirmed cases the test showed the pancreas below normal in thirty-nine, and of these the pancreas was definitely stiffened in thirty-four. Of these fifty-five cases but six returned with symptoms simulating the former ones, a reduction of from 51 per cent of failures in 1926 to about 9 per cent, which in my opinion was due to the value of the pancreatic test in discerning the case which has a "hit of the pancreas", functional congestive or fibrous, and which always convicts the case as a surgical one in the first instance and positively after a course of treatment if the pancreas does not enhance in efficiency. In the six that returned with symptoms, together with thirty-seven more that had been cholecystectomized before I saw them, some very interesting clinical data were gained. Reporting on the six above referred to, five had a stiffened pancreas at operation and one was reported as negative. Numerous tests were made on the first five after operation, proving the pancreas to be always low, and all of these did well symptomatically on alkalis, pancreatic therapy and diet. In the thirty-nine

cases in which the units were low and excepting the six mentioned, it was proven that after cholecystectomy the pancreas became efficient in from three weeks to three months time. In the six mentioned the sac was removed too late and the pancreas had already become fibrous, thus, in operation for gall bladder pathology in which a distinct stiffening of the pancreas is noted, one should be a little guarded in a prognosis of positive relief of symptoms. Disorders of the pancreas alone may give symptoms that so closely simulate gall bladder pathology that differentiation between the two clinically is not possible and cannot be made until the gall bladder has been removed and the pancreas tested. After operation if symptoms return the pancreas should be considered as a factor of cause, as well as adhesions and retained stones, and the pancreas should be tested after operation in these cases for a pancreatic solution of the cause of symptoms as well as before operation to help separate the surgical from the medical type of case. It may, therefore, be noted that since the test became routine in gall bladder work the percentage of operations on the whole has lowered in favor of medical handling, as well as the percentage of success in operation. Individual instances of each of the above are represented in deductions in the following in which there were numerous instances, some of which have already been reported (5).

In March, 1924, a woman of 54 years complained of symptoms due to menopausal arthritis. She began to lose weight and strength in the latter part of 1926. Four pancreatic tests showed 2 units. In Febru-



ary, 1927, she became jaundiced with distinct symptoms of gall stones. On the day before the cholecystectomy was done (April, 1927) her units were still 2. The gall bladder containing stones was removed and the pancreas was found to be hard. Nine weeks later her units were 10 and in the fourteenth week there were 14 units.

**Note** Gall bladder disease with congested pancreas and restitution of pancreatic efficiency.

A man 39 years of age had distinct history and findings of gall stones. His units regularly were 4 on several occasions. Cholecystectomy was done, stones and stiff pancreas found. His pancreas was tested over a year's time, the units always remaining 4. By dieting and pancreatic feedings his complaints were controlled and his general health held up, but there could be no let-up on these for more than a period of five days. Lately sugar has appeared in his urine at times when he has not taken pancreas.

**Note** Gall bladder disease, operated upon too late to save the pancreas and obviate a possible diabetes. Chronic pancreatitis.

A woman 44 years of age with warranted history and suggestion of gall stones was operated upon, cholecystectomy being done and no stones were found on operation. No report possible on condition of pancreas, operation being performed eight years ago. Clinical symptoms similar to those before operation continued over the intervening years. Pancreas 2 units. Diet, alkalies and pancreas therapy most helpful. Occasional glycosuria.

**Note** The case was either an infected cholecystitis causing persistent fibrous pancreatitis, or as is more probable, an original diseased pancreas with symptoms simulating gall bladder pathology.

*Hypopancreorrheic states, organic, non-diabetic.* This heading is used to encompass a group of indefinite cases and the few in number that are more definite in symptoms. Operations and

postmortems show that induration and nodulation of the head of the pancreas are found in 80 per cent of all adults. It is true that in the vast majority of these no symptomatic evidence of pancreatic inflammation or involvement exists, or at best it is so obscure that the pancreas is not thought of in its production. In them the more definite signs and symptoms already mentioned commonly do not exist, yet there is little doubt but that there is significance in the vague and colloquial digestive symptoms often present. Omitting from consideration such cases as definitely characterize the cholelithic, those secondary to malignancy and diabetic cases, and presenting only what may be termed the dyspeptic, one can divide the symptoms here into two groups, local and general.

*Local* The special feature of these symptoms is that they more particularly are intestinal rather than gastric and have already been described under the functional types. All of the digestive symptoms represented in many different types of cases have been seen.

*General* Of this group the most conspicuous symptoms are loss of weight and difficulty in restoring and retaining it. To this, of course, should be added a train of neurotic, neurasthenic and more or less handicapping or partial invalidism states.

The most definite instances of this type are those due to persistent fibrous changes from neglected gall bladder pathologies, and those which accompany malignant or granulomatous diseases of the pancreas itself.

The diagnosis here should be arrived at by the presence of symptoms suggesting pancreatic disease in addition to the pancreatic test, or the test alone carefully performed, stool and urine analyses are sometimes helpful. A word on therapy is worth while here. Late in the disease of inter- and intra-lobular pancreatitis but little can be done, but before this stage much help may be brought about by diets that sharply control the starch intake with complete hydrolysis and dextrinization. The ingestion of from 100 to 250 grams of pickled pancreas a day, a good quality of pancreatic powder in larger than usually given doses and the triple strength enteric-coated pancreatin tablets as suggested by Sansum and put up by one of the pharmaceutical concerns, with or without fair sized doses of some of the alkalis may be effective.

*Hypopancrconic states, organic, diabetic.* Attention has repeatedly been drawn to the incidence of diabetes in gall bladder disease and to the frequency of gall bladder conditions in diabetes. Joslin particularly has drawn attention to this (6) and I have seen one case that became sugar free two months after cholecystectomy for stones was done and which has remained so on a generous diet up to the present, now nineteen months. Surgeons have reported the incidence of glycosuric states in gall bladder disease, Deaver having reported 5 per cent in a large series. These facts, with the incidence of involvement of the pancreas in gall bladder diseases, and now the findings with the pancreatic test, show distinctly that pan-

creatic disorder secondary to gall bladder pathology must always be searched for in the story of diabetes. Since gall bladder diseases are so much more numerous than instances of diabetes, and diabetes may exist without stiffening of the gland, the reason for the greater incidence of glycosuric states in gall bladder disorders is perhaps explained in that there are fewer islands of Langerhans in the head than in the body and especially in the tail of the gland. Injury to the head of the organ as a result of infection of the gall bladder is presumably less constant in the production of glycosuria than in true diabetes, and probably this has something to do with diabetes which is associated with gall bladder diseases being more mild than the average case of diabetes. Joslin has repeatedly said—"If one could pick out the best kind of diabetes to have one would pick out gall stone diabetes."

Working on the suggestion of what may be called for distinction—true diabetes, the external secretion of the pancreas was studied to see if it would show a change from normal. Fifteen cases of well confirmed diabetes were studied. Of these two had high normal units (20 units each) and two were slightly less than normal (8 units each). In all the rest the units ranged from none to 6. The average unit reading in all was 5.3-5 with 3.1-5 units in the main 13. Thus the units were below normal in 86, 33 per cent of all and normal in 13, 13 per cent. At once this is a striking finding, especially in that the two who had high pancreatic readings were easy cases to control dietetically, while all of the rest required insulin in large or small

doses. If this finding is confirmed it promptly brings up the interesting query as to how much of a digestive disorder diabetes is, as well as how much is it only a metabolic one? May not a factor be that because of deficiency of the external secretion of the pancreas, the molecularly proper end sugars for glycogen storage in the liver and muscle cells are not manufactured to completion of intake, and thus, being more or less foreign to the tissues, they are incapable of storage and flow over into the blood stream? Such incomplete sugar is still capable of oxidation by insulin or complete elimination from the body. It is considered that the islands in function are more or less apart from the acinus cells and that diabetes is only an island affair. But pathology in diabetic cases shows that usually the whole gland is involved, and if only the island cause is considered (as seems to be generally held) how is it that in gall bladder diseases (which causes a general pathology in both cells and mostly in the head where the acinus cells predominate) that glycosuria is so often met with?

In our group of thirteen severe cases, attention directed to the external secretion of the gland evolved most striking results in reduction of insulin units with benefits in general health taking place. It has been reported elsewhere (4) that in five of these there was much difficulty in holding the urine sugar free on diets which approximate basal metabolism without considerable sized doses of insulin. In all of them when put on pancreatic feedings in doses of from 100 to 250 grams a day, from about the second

or third day on, a marked reduction of insulin with distinct general improvement in health, strength and well being took place in each case. In four others this result was not so striking in insulin reduction but in nine of them it was definite. In the other four no worth while result could be noted, these four strangely enough having three in which units were relatively high—4, 4 and 6, and but one with no units. With experience in six more recently studied cases I am now of the belief that the external secretion of the pancreas cannot be totally neglected as it has been in the past in handling diabetic cases. The external secretion of the gland has a distinct significance etiologically, diagnostically and therapeutically\*. This is not true in all instances of diabetes, but it certainly is in a large enough proportion of cases to be most important. No instances of hemochromatosis were studied, these being considered as a too irregular type of diabetes because of liver and iron metabolic disturbances.

*Hypopancræorhelic states, malignant and granulomatous.* Of cancer, sarcoma, syphilis and tuberculosis, cancer is the most common. All excepting sarcoma occur mostly in the head of the gland, and it is because the pancreas to its so-called neck comprises the largest portion of the gland and is the part mostly concerned in the external secretion, that lowered or absence

\*Argument has been presented that in pancreatic feedings the islands of Langerhans (and thus insulin) are ingested. If insulin is destroyed in the stomach this cannot prevail, and at best the amount that would be taken would be too small to accomplish the results observed.

of deficiencies would be met with in these conditions

As far as is known, no instances of tuberculosis have been encountered, although it is possible that the not uncommon miliary tuberculosis of the pancreas associated with acute or chronic tuberculosis was met with in one instance which was absent of units. The pancreatic efficiency here is usually low in the advanced case because chronic pancreatitis is not an uncommon associate of tuberculous lesions of other organs.

Syphilis of the pancreas is found in about one-fourth syphilitic newborn infants, and the pancreas is rarely the seat of gummata occurring in the acquired form. It is most probable that acquired syphilis only very rarely causes chronic pancreatitis.

Cancer of the pancreas may occur anywhere in the gland, but is twice as frequently confined to the head as in the whole gland or other localized parts. Those of the head and whole gland comprise about 94 per cent of all instances, and it is most probable that deficiency states of external secretion are the rule. In the two instances studied both were totally hypopancreorrheic on several tests in each.

Sarcoma was met with in one instance, it involving the tail and the body. In this instance normal units were present, probably because the head was not involved. No instances of adenoma were met with.

#### CONCLUSIONS

The author's pancreatic test has been employed in over fifteen hundred patients and has been found to be useful

clinically. The best stimulant is peptone solution and one of magnesium sulphate serving as a fair second providing bile flows. Practically all of the tests used formerly are of little value clinically, most of them being positive in negative cases and negative in positive cases.

A practical classification of hypopancreorrheic states is offered.

The pancreas is a most essential organ in the body and one which is not easily affected by functional neurological or reflex disturbances.

Reduction in its function occurs in some diseases and not in others. It is a factor of importance in cardiac decompensation, arteriosclerosis and some types of digestive disturbance.

In the cases of acute abdominal disturbances isolated hemorrhagic pancreatitis is worthy of inclusion as a subdivision entity of acute hemorrhagic pancreatitis.

Infections of the biliary tract often cause dysfunction of the gland, and the pancreatic index should be studied in all such cases. When uniformly low, "stiffening" of the head of the gland should be suspected, and in the stone as well as the non-stone cases operation is called for in most of these instances. After cholecystectomy with a return of symptoms the pancreas should be considered as a causative factor and the efficiency of the gland tested.

Internists and gastro-enterologists should consider disorders of the pancreas as a cause of digestive symptoms and adopt appropriate treatment where hypopancreorrhea exists.

The external ability of the pancreas should be studied in diabetics. In 86

per cent of our cases this was deficient, and this deficiency is an important factor both etiologically and therapeutically in the handling of the diabetic

In malignant and granulomatous states it depends upon how much of the head of the gland is involved as to whether the external secretion would be deficient or not

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- (2) OPIE, EUGENE L Diseases of the Pancreas, Cause and Treatment  
(3) BASSLER, ANTHONY Archives of Internal Medicine, February, 1925 Vol 35, pp 162-174  
(4) BASSLER, ANTHONY Archives of Internal Medicine Ibid  
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(6) JOSLIN, ELLIOTT P The Treatment of Diabetes, pp 476-477

# Present Results and Outlook of Diabetic Treatment\*

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**D**IABETES is a subject of perennial interest. The topic selected for me is in the nature of a review, which is timely, because at present we have reached a point where some old questions are apparently decided and new ones are just beginning to be opened up by research.

## Diet

The first part of diabetic treatment is necessarily diet. This is the most important and fundamental part and the only one which must be employed in every case. The components of the diet requiring consideration are protein, carbohydrate, fat, and finally total calories and body weight.

Protein has been the subject of past disputes which now appear to be settled. Various authors have claimed that protein is specifically toxic for diabetics, possibly even more harmful than carbohydrate, and that it should be limited to very low quantities in the diabetic diet. These contentions were never proved and may now be regarded as definitely exploded. There is no specific toxicity of protein for diabetics, and no influence beyond its

caloric value and its content of potential carbohydrate. It need not be closely restricted in diabetics who are free from kidney diseases or other special complications. It should on the contrary be used fairly liberally, because it gives strength and adds taste and variety to the diet. In our closest restrictions in uncomplicated cases without insulin, we never use less than 60 grams of protein for the permanent diet and habitually use as much as 80 grams. In milder cases or for persons especially fond of protein, it is possible to raise the allowance to 100 or even 120 grams per day, seldom more. The form in which the protein is given is considered immaterial.

Carbohydrate has been subject to wide extremes of variation in the past, ranging from almost complete elimination in the classical diets to the almost exclusive carbohydrate rations represented in oatmeal and related "cures." Similar divergences have continued almost to the present time. In the high fat diets which were recently prevalent, carbohydrate was limited to the least possible proportions, perhaps 30 to 60 grams per day. On the other hand Sansum has shown that patients under insulin treatment may sometimes receive quantities up to several

\*Read before the American College of Physicians, New Orleans Clinical Week, March 8, 1928.

hundred grams of carbohydrate per day with no great increase in the insulin requirement. Our own practice is intermediate in this respect, allowing seldom less than 50 grams of carbohydrate in the permanent daily diet of a patient without insulin, and more often about 80 grams as a rule. In milder diabetics or under special conditions the carbohydrate may be increased to 100 grams or even higher. The reason for avoiding the highest proportions of carbohydrate is not that the insulin requirement is unduly raised, but rather that the fluctuations of sugar are too marked. A smooth regular control of the blood sugar is more readily achieved when the carbohydrate is limited as mentioned.

Fat furnishes the greater part of the calories in all standard diabetic diets, and the so-called high fat diets merely carry the use of it to an inconvenient and harmful extreme. These diets, which recently were a fad widely prevalent in this and other countries, were based upon the belief that fat is harmless in diabetes, or that the diabetic tolerance is affected only by preformed carbohydrate and by the potential carbohydrate which forms about 60 per cent of the protein molecule and a small part of the fat molecule. It is justifiable to say definitely that this belief is false, because it was never supported by any proof and complete proof to the contrary has been published. The diabetic patient requires regulation of every kind of food, including fat. When protein and carbohydrate are supplied in the amounts already mentioned, we complete the diet with sufficient fat to

make up the requisite number of total calories.

The total calories are the most important factor in the diet treatment of diabetes. This factor is practically synonymous with the body weight, since the number of calories supplied governs the weight of the patient. Before the discovery of insulin, the importance of this principle was demonstrated by the fact that cases which were too severe to be controlled by the former methods could be brought and kept under control by fasting and undernutrition. Since the discovery of insulin, this fact has received mathematical proof. For such an experiment it is best to choose the severest cases with the highest insulin requirement, so that the insulin supply is derived as far as possible from our own injections and as little as possible from the variable source of the patient's own pancreas. If the total calories are kept the same, it will be found that only a slight change in the insulin requirement results from varying the carbohydrate allowance from 30 gram to as much as 200 or 300 grams per day. On the other hand, if the total calories and body weight are increased by the addition of fat or any other food, the insulin requirement rises tremendously. The most important precaution for the permanent control of diabetes is therefore the regulation of the total calories and body weight. The obese patient practically never requires insulin, because by reducing the weight to normal we change the diabetes to a mild form. If the insulin requirement of any patient is excessive or if the fluctuations of sugar cannot be controlled, we can reduce the insulin and

generally obtain smooth control of the sugar merely by reducing the body weight by suitable changes of the total calories

The great majority of cases must be treated by the general practitioner, but no physician should undertake to treat diabetes unless he can calculate a weighed diet. The majority of cases do not actually require weighed diet, because of their mildness, nevertheless, in order to advise intelligently concerning the composition of an unweighed diet, the physician should possess the knowledge of weighed diets and should take care that the ration advised for his patient is properly balanced and not too high or too low in any components. Merely to prohibit sweets and high starches may stop glycosuria for the time being but nearly always results in relapses or other trouble later. When the diabetes is more severe a weighed diet becomes essential. When it is severe enough to require the use of insulin, the diet should invariably be weighed, unless in rare instances the patient becomes able to estimate his food almost as accurately as if it were weighed.

The mere calculation of accurate diets is a simple matter, and owing to its importance it should not be complicated with any superfluities which will make it more difficult for the general practitioner.

There has been something of a fad in the use of respiration apparatus, and if a thyroid disorder is present or suspected the determination of the basal metabolism may of course be instructive. But for the treatment of any ordinary cases of diabetes it should be understood that respiratory

determinations or basal metabolism tests are unnecessary. There is no reason for planning an initial diet according to the basal requirement. There is no accuracy in determining the basal rate and then guessing at the calories needed for exercise. One may as well guess at the entire requirement in the first place. It is best in the majority of cases to undernourish the patient more or less at first, while sugar and acetone are being cleared up. The diet is increased slowly or rapidly according as the patient happens to be over or under normal weight. In the long run the number of calories needed is determined by the body weight. A diet on which a patient continues to lose is insufficient. A diet on which he continues to gain is excessive. The right diet is the one which permanently maintains the desired weight. This rule is simple, but there is no ultra-scientific substitute for it.

Another of the recent fads, namely the calculation of the so-called ketogenic-antiketogenic ratio, is likewise unnecessary. This practice arose from a false view of diabetes, namely the belief that only carbohydrate affects the diabetic tolerance. In other words, the strain upon the pancreatic function was supposed to be measured by the total potential carbohydrate of the diet, consisting of all the preformed carbohydrates, plus about sixty percent of the protein, plus about ten percent of the fat. Fat was imagined to be harmless except for the production of acidosis. The ideal diet was then conceived to be the one which would supply the highest nutrition in the form of fat calories without giving rise to



acidosis The purpose of calculating the ratios between the fatty acid and carbohydrate components of the diet was therefore to supply a maximum of the former with only such a minimum of the latter as was necessary to prevent acidosis This doctrine was never supported by any proof, and it disregarded the complete disproof which already existed in the form of experiments published in conclusion with the undernutrition treatment The introduction of insulin furnished a further means of exposing the fallacy as above mentioned When the total calories are kept unchanged by substituting carbohydrate for fat, it is an easy matter to confirm Sansom's recent reports by demonstrating that the carbohydrate allowance may be varied widely with surprisingly little change in the insulin requirement—sometimes no change at all On the other hand, when the total calories are greatly increased by adding fat, and especially if the body weight is thus markedly increased, the increase of the insulin requirement may be slow and gradual but it becomes enormous We thus return to the fact which was proved years ago, namely that the total calories and body weight are the chief factors determining the insulin requirement or the burden upon the pancreatic function Neither fat, alcohol nor any other source of calories is harmless or can be disregarded The purpose of limiting fat is not merely to prevent acidosis but to limit the total calories There is no reason ordinarily to restrict protein or carbohydrate to an extreme minimum As mentioned I do not generously favor the extremely high proportions

of carbohydrate, because the fluctuations of blood sugar are harder to control But for certain special purposes this information is of great value, for example, in giving a diet consisting chiefly of carbohydrate to a diabetic with cirrhosis of the liver Ordinarily, what is desired is a rationally and agreeably balanced diet There is considerable leeway for individual preference, so long as the total calories and body weight are suitably regulated With any possible proportion of protein and carbohydrate that may be chosen under the principle here explained, the occurrence of acidosis is impossible, and ketogenic-antiketogenic ratios should be forgotten

#### INSULIN TREATMENT

Though insulin justly ranks as one of the greatest discoveries of medical science, its use should be avoided whenever possible This advice is not based on any danger in insulin, for there is no danger which should deter anybody from using insulin when it is actually needed The danger of hypoglycemia has been exaggerated It is a discomfort or even a distressing affliction to the patients and families in a small proportion of specially difficult cases A few deaths have been reported from this cause, but as a rule under avoidable conditions We have had no such fatalities in our entire series of cases and the chance of such is trivial in comparison with all the other dangers of diabetes

The reason for avoiding insulin treatment is its inconvenience It is a mistake for patients to think that by taking insulin they can avoid a strict or weighed diet The need of an ac-

curate diet is increased by insulin. Under treatment by diet alone, only glycosuria or hyperglycemia is to be feared. The patient may estimate or vary his diet at will so long as he keeps it low enough. A slight excess may be balanced by extra strictness preceding or following it. With insulin there is the additional risk of hypoglycemia, and the general results are poor unless the diet is kept rigidly exact and uniform.

Insulin should never be given to obese patients unless temporarily for some special purpose, because the simple reduction of the weight to normal will nearly always convert such cases into a very mild and easily managed form. As a general rule in other cases, if moderate undernutrition will control the diabetes, it is preferable to keep the patient a few pounds below the average normal weight than to burden him with insulin injections. The chief exception is in children, for even if their diabetes is in a mild incipient stage they are generally safest with a little insulin as a precaution against progressiveness. Also in some border-line cases in adults, when the patient is barely getting along with uncomfortable privations in the attempt to avoid insulin, it is sometimes helpful to give insulin for some period because the more thorough pancreatic rest thus afforded assists the gain of tolerance, and paradoxically in some instances the temporary giving of insulin is the means of permanently avoiding it. But whenever the diabetes is sufficiently severe, and management by diet alone entails any serious degree of emaciation, disability or

discomfort, insulin should be resorted to without hesitation.

We still adhere to the ideal of keeping the urine sugar-free and the blood sugar normal at all times. This involves questions of the total dosage and the number of injections per day. It is best to regulate the diet and body weight, as already stated, so as to keep the total dosage as low as possible. The number of injections may thus be reduced in the milder cases. In the more severe cases the fluctuations of sugar, the alternations of glycosuria and hypoglycemic attacks are much less troublesome when the total dosage is kept low. The number of injections into which the day's dosage is divided in any case can partly be predicted from experience, but largely must be determined by trial. In the milder cases one injection, usually at breakfast time, may suffice. With increasing severity the point is reached where increase of the single dose no longer gives ideal control of the sugar, either glycosuria or hypoglycemia occurs. The required insulin must then be divided into two doses usually given at breakfast and supper. With still greater severity, three doses may be needed, and in rare juvenile cases four doses. In this connection two practical rules of insulin action may be remembered. The larger the single dose of insulin the less is the effectiveness of each unit in it. The greater the number of injections in a day, the smaller is the total amount of insulin required.

The chief difficulty encountered, especially in the severest youthful cases, is the tendency to hyperglycemia or glycosuria toward morning, and to hy-

poglycemia toward evening. Members of the Toronto school first introduced the practice of giving insulin with meals, thus crowding all the insulin usually into eight to twelve hours and leaving a long night period of 12 to 16 hours without insulin. The suggestion of concentrating most of the carbohydrate in certain meals does not obviate the difficulty in severe cases. In general, it should be remembered that there is no fundamental reason for giving insulin with meals. Insulin is needed for the metabolism of food, not for digestion. It is therefore required through the entire 24 hours. Also I called attention long ago to the fact that the insulin requirement is not correlated with the mere level of metabolism. For example, heavy exercise raises total metabolism and lowers the insulin requirement. (Incidentally, this again illustrates the folly of beginning treatment by prescribing a "basal" diet and minimal activity in order to keep metabolism lower.)

Apart from intentional experiments, it will sometimes be noticed that a child on a constant program of diet and insulin will show glycosuria on a rainy day with quiet life, and hypoglycemia on a bright day with strenuous play. Ignorance of this simple principle seems to have been responsible for the misconception that the lower metabolism during sleep at night should be accompanied by a lower blood sugar and a smaller need for insulin as compared with the active day period.

In milder cases insulin may be given with meals as a matter of convenience, and with this assistance the patient's own pancreas will tide over the inter-

val without injections. But in the more severe cases referred to, the rise of sugar during the night should be prevented by more equal spacing of the doses. In rare instances, there is no way of smoothly regulating the sugar except by a fourth dose of insulin about midnight. Nearly always, however, it is sufficient to shorten the night interval by giving the morning dose 30 to 90 minutes before breakfast (or as early as possible without causing hypoglycemic attacks) and the evening dose an hour or two after supper or at bedtime. The exact details must often be worked out by trial in the individual case.

By means of insulin in conjunction with proper diet, it is theoretically possible to enable every diabetic, in whom fatal complications do not already exist, to live out his full natural lifetime. Specialists and all others who write on this subject in medical journals invariably describe the life-saving effects of insulin in all types of cases. Yet it has been one of the most unpleasant surprises to find that diabetic mortality figures published both in this country and in England have shown no fall since the discovery of insulin. The reason must evidently be sought either in a failure of physicians at large to use insulin properly, or a failure of patients in general to follow the instructions properly. The remedy for this condition seems to be largely a responsibility of the general practitioner, who should either control his diabetic cases effectively or refer them to somebody who will do so. It is sufficiently demonstrated that the careless or unskilled use of insulin

does not save diabetic lives in the long run

#### TREATMENT OF COMPLICATIONS

The chief complications requiring consideration are acidosis, gangrene and infections. The most important treatment is prophylactic, for if all cases of diabetes were well controlled from the outset there would be practically no diabetic coma or gangrene. Under existing conditions it should be emphasized that now, as formerly, these complications are the chief causes of death in diabetes.

#### ACIDOSIS

There is little new to say on the treatment of coma, present or impending. Most important is the use of maximum doses of insulin, often amounting to more than 200 units in 24 hours. Only second to this is the administration of the largest possible quantities of fluid, because the tissues in acidosis are dangerously desiccated and because water is needed for abundant diuresis. Fruit drinks are usually preferred for this purpose, because they can be taken in large volume with the least tendency to nausea, and because they also supply carbohydrate. Coffee or tea with sugar, or anything else that will furnish water and carbohydrate acceptably, may be used. There seems to be some perplexity as regards the need of supplying sugar to a patient who is already overloaded with sugar. But we wish to use insulin in huge doses and the plentiful administration of sugar is a safeguard against hypoglycemia. For the immediate time we have no interest in stopping glycosuria, but only

in stopping acidosis, provided enough water is present the excess of sugar is harmless and even makes a useful diuretic. In particular, according to the laws of metabolism, increased sugar supply makes increased combustion, and in this way also the giving of sugar assists in getting rid of acetone. If the patient's stomach is unable to retain fluid to the extent of 5 liters or more in 24 hours, saline or glucose solutions should be given rectally and intravenously. Hypodermoclysis requires rigid asepsis to guard against the serious danger of infection. Intravenous injections carry no such danger, and in a critical case, in preference to delaying several hours, it is justifiable to inject a clean filtered solution intravenously without sterilizing, because infection never results. But the volume of intravenous fluid should be gauged with regard to the strain upon the weakened heart. Alkali is less important since the introduction of insulin, but my personal belief is that sodium bicarbonate is helpful in moderate dosage, (5 to 20 gm total) in cases with much reduction of the plasma bicarbonate or much dyspnea. Keeping the patient warm, emptying the stomach or bowels, and attention to any infection or other complications, are routine measures according to conditions. Most drugs are useless, caffeine, digitalis, or other cardiac stimulants may be indicated because of the grave circulatory factor in severe cases, but it is questionable whether they can often change the outcome.

A frequent cause of death nowadays is the form of acidosis which often occurs suddenly in insulin-treat-

ed patients who have glycosuria. It commonly begins with abdominal pain and vomiting and progressive weakness, and the classical symptoms of dyspnea and dim consciousness may not be manifest until a hopelessly fatal stage has been reached. A differential diagnosis is sometimes necessary between this condition and a hypoglycemia attack, one demanding insulin and carbohydrate, the other carbohydrate without insulin. The distinction is readily made by the symptoms, and by the finding of high sugar and acetone in the urine or (if the kidneys are highly impermeable) in the blood. Incidentally, the nitroprusside test of the blood plasma, which can be performed at the bedside if necessary, is probably the quickest and surest index of the condition and progress at the various stages in any type of acidosis.

The time element is so vital in combating acidosis, that one of the most important phases of the treatment may be that which is prescribed by telephone, in instances when there may be a delay of an hour or more before the doctor can reach the bedside. The history and description of the symptoms often suffice for a diagnosis, which is further strengthened if a member of the family tests the urine for sugar and reports it heavy. Sometimes insulin is available and a dose of as much as fifty units can be ordered immediately. Under any circumstances the forcing of fluids and carbohydrate can be started. Regarding insulin, a well-informed physician could rarely make a mistake which would involve any actual danger if he were to arrive within an hour

or two to give antidotes in the form of sugar or epinephrin if needed. On the other hand, every delay in beginning treatment will involve an appreciable increase in the mortality of acidosis. When too long a time elapses the patient reaches a fatal stage, in which strenuous treatment may clear up sugar and acetone and raise the blood alkali, but death nevertheless occurs with symptoms resembling shock.

Diabetic gangrene has a double basis, namely, a specific deficiency of healing power in the tissue, and deficiency of blood supply due to arteriosclerosis. Sometimes only one of these causes is present. For example, diabetics with uncontrolled sugar are subject to local infections, necrosis, and septicemia from trivial injuries in the lower extremities or any part of the body, and the term gangrene is applied to many of these conditions in a loose sense. Also, true gangrene may rarely develop in a diabetic whose blood sugar is kept fully normal under treatment, merely because arteriosclerosis is present to an extent that will cause gangrene also in a non-diabetic. The rarity of this occurrence must be emphasized, because the onset of gangrene in a diabetic without glycosuria is generally explainable by the presence of hyperglycemia, and this is one of the reasons for insisting upon normal blood sugar even in the elderly. The development of arteriosclerosis in diabetics may be of interest in connection with the involved problem of the etiology of arteriosclerosis in general. It is present in every diabetic who has had active glycosuria for a sufficiently long time—perhaps

10 years, more or less. Even with the mildest diabetes, in which the patient may make light of his glycosuria because it goes on seemingly with no symptoms or harm for a seemingly indefinite time, arteriosclerosis is inevitable, and the patient should be warned that his arteries are thickening year by year and he is becoming more liable to gangrene and other vascular complications. After the circulation has become seriously impaired, for example when examination shows that pulsation in the dorsalis pedis artery is feeble or absent, it becomes important to insist on strict cleanliness, warmth and general care of the feet, and the utmost avoidance of the slight injuries (abrasions, trimming of corns, etc.) which afford the commonest starting points of gangrene. But the diabetes should be emphasized as the great cause back of everything, and when the sugar is thoroughly controlled before the arteries have become too badly occluded, other precautions may be disregarded because there is no greater tendency to gangrene than in a non-diabetic.

The medical treatment of gangrene is by diet, aided usually by insulin. The best diet is one consisting largely of protein and carbohydrate, for example, 50 to 80 gm protein for maintaining strength, 80 to 120 gm carbohydrate for guarding against the increased danger of acidosis in such conditions, and closely restricted fat to make up a total ration of 600 to 1,200 calories according to the individual case. This advice is contrary to the natural prejudice in favor of a high diet for repair of tissue or resistance to infection. But as a rule an increase of diet above the low fig-

ures mentioned belongs only to the final stage of recovery. The majority of the patients are overweight, and even in an exceptionally emaciated case these figures should be only slightly exceeded. There is little tendency to losing weight with the patient in bed, and it should be understood that several weeks of moderate undernutrition during the stage of infection and granulation creates by far the best condition for resistance and healing. It should be strongly emphasized that high diet plus high insulin dosage to control the sugar does not give equivalent results, and comparison of the two methods shows that an overfeeding program, especially with high allowances of fat, will needlessly sacrifice many lives.

As an incidental feature, we now at this Institute make the diet salt-free in gangrene cases. Many of these cases have more or less local swelling, and the reduction of this edema by salt exclusion distinctly improves the circulation. Some of the patients have more or less hypertension, and thus the salt-free diet is indicated. Hypothetically, the mere existence of arteriosclerosis may also be regarded as an indication. The salt restriction is subsidiary in importance as compared with the control of the sugar by diet. But we believe that it improves our results, though this impression could scarcely be supported by figures.

Besides diet, insulin is needed in the great majority of these cases, because quick and radical control of the sugar is of crucial importance. Also, the intoxication from the gangrenous area makes the sugar more difficult to reduce and intensifies the need for insulin, so that surprisingly large quan-

tities may be required temporarily in cases which, after cure of the gangrene, have excellent tolerance without insulin

This toxic effect is often perceptible in cases with only a small black spot on a toe, without fever, malaise or any other suggestion of systemic reaction. It reaches an alarming point with sepsis and fever, when there may be difficulty in keeping the sugar normal even with dosage above a hundred units of insulin daily. The progress of the gangrene can almost be judged by the insulin requirement alone. Reduction of the required insulin indicates healing. On the other hand, a sharp rise of the insulin requirement is strongly significant of spreading gangrene and increasing intoxication. Sometimes when the condition appears satisfactory, with no visible enlargement of the gangrenous area and no fever or malaise, the blood sugar tests may show a rise which is barely controlled by increases of 10, 20 or more units of insulin. Unless some other cause can be discovered, it may be considered practically certain that the gangrene is spreading in the deeper tissues, and operation should be advised immediately instead of waiting for the graver manifestations which will surely appear soon.

As a general rule, with occasional exceptions, gangrene will heal under the medical treatment outlined if the necrosis or infection has involved only the superficial tissues. In other words, when the specific deficiency of tissue resistance is corrected by controlling the sugar, healing can be obtained in spite of poor circulation. Extensive deep infection or necrosis involving

bones, joints or tendons will sometimes get well if there is an ample blood supply as indicated by strong pulsation in the dorsalis pedis or other vessels of the foot. With the usual advanced arteriosclerosis present, a small gangrene involving tendons or bone will heal in a minority of instances. Simple dry dressings usually suffice, or some mild wet dressing for pus. Attempts to use antiseptics or even Dakin's solution may sometimes extend the necrosis. Electric light treatments, baking, or brief soaking in warm water may sometimes be beneficial but sometimes are distinctly harmful. Absolute rest of the foot is most important, the patient being kept either in bed or in a chair with the leg horizontal.

Surgical intervention is required nearly always when there is deep extensive gangrene or extremely poor circulation, and also in the majority of average cases where there is any necrosis of tendons or bone. The tendency nowadays is in the direction of surgical conservatism, but nevertheless it should not be forgotten that amputation at or above the knee is sometimes the most conservative procedure from the standpoint of saving life. There is not space to discuss the detailed indications, which need to be judged in each individual case by somebody with adequate experience.

By the best methods now available, patients with dangerous sepsis are frequently saved, though the mortality in such cases remains high. On the other hand, nearly all patients with simple gangrene can be saved, the exceptions consisting almost entirely of deaths due to the age or other general conditions independent of the diabetes.

The broad principle for the treatment of all local or general infections is to control the diabetes thoroughly and in addition use the same medical or surgical measures as in a non-diabetic. For carbuncle I favor conservative methods as opposed to radical excision. Tuberculosis remains one of the most serious complications, and it stands alone in requiring treatment with high caloric diets and frequently high insulin dosage to correspond. With this treatment the prognosis of the tuberculous diabetic is no longer hopeless as heretofore, but is fully as good as that of the non-diabetic with a similar infection.

#### NEW DIABETIC REMEDIES

Attempts to administer insulin by mouth have yielded nothing of practical value. All other remedies tried or recommended in the past as having a specific influence on diabetes when taken orally must be classed as failures.

Recently attention has been attracted by the guanidine derivative, called synthalin, synthesized by Frank and collaborators in Minkowski's clinic at Breslau. The European reports leave no doubt that synthalin will reduce blood sugar in a manner somewhat like insulin. It may still be uncertain whether the benefit from such reduction of sugar is fully equivalent to the effect of insulin. At any rate, the toxicity of the new compound is such that it can be used as a substitute for insulin only in moderate quantities. The discoverers do not claim that it can entirely replace insulin in cases of any considerable severity. If it merely permits decreasing the number of insulin injections it will be a boon to

many patients and a valuable advance in therapy, but its status must still be regarded as experimental.

The vegetable material called myrtillin was discovered by Richard I. Wagner in Vienna, and has been tested here experimentally and clinically. The entire laboratory investigation has been conducted by Wagner and he is entitled to the full credit in respect to both planning and execution. I have not been able personally to participate in this fundamental phase of the work or to check up its accuracy by any direct observations of my own, but since competent workers in other laboratories have reported confirmations in all details, it seems fair to assume that the findings are correct. If it be thus admitted that myrtillin can influence the assimilation of sugar in the normal organism and can produce benefits in partially and totally depancreatized dogs, there is a reason for making trials in clinical cases of diabetes. These trials have apparently shown beneficial effects in a number of patients, as well as negative results in a considerable number of others. Severe cases seldom give any indication of a favorable response to myrtillin, unless it be sometimes in the form of a diminished tendency to hypoglycemic attacks from insulin. The milder cases in older individuals offer the best chance of success, but unfortunately these are also the ones in which a positive demonstration of results is most difficult. Because of the well-known changes of tolerance which occur irregularly in the early stages of treatment, we have based our opinions chiefly upon the apparent results in a limited number of cases which had already been observed for



long periods under reasonably accurate conditions. These observations have been summarized in our earlier publications and will soon be published in detail. On the whole the experiences reported by other physicians who have tried myrtillin have been more favorable than our own, perhaps because they have dealt with a larger proportion of mild or otherwise suitable cases. At the same time a few of the best qualified judges, who have investigated myrtillin in the friendliest spirit, have obtained negative or unconvincing results—whether because of the refractory character of the cases in their series remains to be seen. It must be plainly recognized that the clinical tests do not afford a positive demonstration scientifically. If the animal experiments could be overthrown, it might be possible to discard all the clinical evidence as representing mere accident or coincidence. But if the influence of myrtillin upon experimental diabetes and upon the carbohydrate metabolism of normal animals and persons stands as scientifically established, there is some probability added to the view that the apparent clinical benefits are real and some burden of proof is placed upon anybody who would dismiss them as mere coincidence. Such a host of diabetic remedies have been enthusiastically recommended for a time and then been consigned to oblivion, that the utmost caution is necessary in affirming that anything has actual value, but on the other hand the worthless remedies have never been supported by valid animal experiments. We fully endorse the action of the A. M. A. Council on Pharmacy and Chemistry in withholding approval of myrtillin

pending fuller investigation, because the widespread exploitation of a useless medicament would be a misfortune. It is at least beyond question that myrtillin is harmless, and the mere swallowing of a tablet three times a day is not even an inconvenience to the patient. The investigation of the material in a number of selected clinics therefore seems to be the right procedure at this stage. It should be made clear in advance that myrtillin is not insulin or a powerful substitute for insulin, that its action if real is not spectacular and will not revolutionize the general methods or results of diabetic treatment.

The world-wide movement in the direction of oral medication seems to represent the chief tendency in recent diabetic research. From the scientific standpoint insulin is the specific and ideal remedy. But the weighed diet and the hypodermic injections are irksome to patients, and human nature itself must furnish much of the explanation why the ideal diabetic remedy has thus far made no perceptible change in mortality figures. If anything can be found which will offer a more convenient and agreeable way of controlling diabetes, it will probably be an aid to some extent in reducing the death rate.

In conclusion, it is theoretically possible to enable diabetic patients to live as long and almost as efficiently as if they had never had diabetes, provided treatment is begun at a reasonable time and is carried out with reasonable thoroughness. It is the task of the medical profession to accomplish the practical realization of this ideal so as to reduce the present high mortality from this disease.

# The Occurrence of Anemia in Myxedema\*†

By CHARLES T. STONE, B A , M D , F A C P , *Galveston, Texas*

WHEN William Gull, in 1873, first described the disease which Ord, in 1877, designated Myxedema, a clinical picture so comprehensive as to scope and accurate in detail was given to the profession that little was left for subsequent generations to add. Murray's successful treatment of a patient with the disease by the subcutaneous injection of a glycerine extract of thyroid gland, in 1891, so completed the knowledge upon the subject that nothing of value was added, excepting the oral administration of thyroid substance, until in 1893 it was shown by Magnus-Levy that there is great and constant lowering of the basal metabolic rate. Thus there was constructed a clinical knowledge of myxedema by which physicians have come to recognize it as a definite though relatively uncommon cause of disability.

From the clinical point of view the recognition of typical examples of myxedema is comparatively easy, but from time to time cases are encountered in which the more characteristic

symptoms and signs are not so manifest, and in which the real nature of the illness is obscure. In such instances the dominant finding is frequently a severe or moderately severe anemia which may be erroneously interpreted as the cause rather than the result of the illness. There are now fairly numerous clinical reports of cases of myxedema in which an anemia was the most conspicuous feature, as for example those of MacKenzie (1), Janney and Engel (2), Baker (3), Warfield and Greene (4), Minot (5), Emery (6), and others. Strangely enough in many of the reported cases with marked anemia the more common and readily recognizable symptoms of myxedema were inconspicuous.

## EXPERIMENTAL STUDIES

From the experimental side there is evidence in support of the belief that marked reduction in the function of the thyroid gland is often followed by a depression of the erythropoiesis in the bone-marrow. Esser (7) has reported the results of his studies upon dogs and rabbits subjected to total thyroidectomy. Following the operation the animals showed a progressive lowering of the number of red blood cells and the percentage of hemoglobin. Experimental studies by Kishi

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(8) and Mansfield (9) produced similar findings, and brought out the additional facts that in the experimentally produced anemias of animals blood regeneration was delayed by thyroidectomy, and that thyroid feeding in normal animals might bring about an increase in red cells and hemoglobin. These experiments were reported between 1904 and 1907, but they appear to have been carefully controlled, and doubtless, the conclusions drawn are well founded. Some difficulty in the interpretation of the results is, at times, occasioned by reason of the fact that some of the animals developed tetany, evidently because of removal of the parathyroids with the thyroid. However, disregarding the instances in which this occurred, the uncomplicated experiments justify the conclusion that anemia may follow a deprivation of the thyroid secretion. The experimental anemia so produced is usually of the secondary type, without the presence of abnormal red cells or striking alteration of the leucocyte and differential counts.

#### CLINICAL MYXEDEMA AND ANEMIA

In order to arrive at some idea as to the incidence of and the facts relative to anemia associated with clinical myxedema the records of all patients with the disease seen in office and hospital practice over the period of the past eight years were reviewed. In twenty-three instances was the information sufficient to permit a detailed study. The blood counts, basal metabolic rates, results of treatment (in some instances) and other essential data are shown in Table I.

The outstanding facts in this group of twenty-three patients are as fol-

lows. All but one were of the white race. Nineteen, or 82.6 per cent, were females, and four, or 17.4 per cent, were males. The average age at the time of observation was 42.7 years; the youngest and oldest patients were 21 and 53 years of age respectively. Basal metabolic rates (22 cases) averaged 30.5 per cent with extremes of minus 17 per cent and minus 45 per cent. A striking observation was a complete lack of parallelism between the basal metabolic rates and the blood counts, although in all four patients with rates of minus 40 per cent or more, some degree of anemia was present. Thirteen patients, or 56.5 per cent of the series, showed a reduction in the number of red blood cells and in the percentage of hemoglobin. The lowest erythrocyte count was 2,750,000, and the highest 5,820,000, with hemoglobin values of 40 per cent and 113 per cent as the extreme variations. The majority of the patients in whom anemia was present showed only a slight or moderately severe change, and in most instances the anemia was of the secondary type. The color index was found to be above 1.0 in five cases, the highest being 1.2. Abnormal red cells were reported but once, and then only anisocytosis and poikilocytosis were observed. In every case, excepting one, the leucocyte and differential counts were within normal limits, presenting no feature characteristic or diagnostic of myxedema. Five cases had follow-up blood counts made after the basal metabolic rate had been elevated by treatment and in each it was found that the cells and hemo-

globin had been caused to approach the normal values

Three patients of the series (Case numbers 5, 15, and 18) presented an anemia as a salient finding and had been treated for anemia elsewhere—two for pernicious anemia (cases 5 and 15) and one (case 18) for secondary anemia—for periods varying from three to nine years. The case histories of these three patients are herewith detailed

#### CASE REPORTS

*Case No 5* Mrs A U, aged 50, a housewife, was first seen September 13, 1922, complaining chiefly of weakness. Except for the death of her mother from cancer, the family history was unimportant. She had always been very healthy, having been confined to her bed only at the birth of her children, and following an operation for repair of a lacerated cervix. A little more than three years previously she noticed weakness, a curious empty feeling in the head and dizziness. In time all of her symptoms became so pronounced that she could no longer perform her usual household duties. A physician found an anemia, which was thought to be of the pernicious anemia type, and she was given iron and arsenic, which she took intermittently for the past two years. She thought the arsenic caused swelling of the face and ankles. All of her teeth were extracted four months before she came under observation.

The patient appeared quite pale, and there was a distinct yellowish tint to the skin. Slight non-pitting edema of the face and extremities was present.

The mucous membranes were pallid. The blood pressure was 110 systolic and 70 diastolic. The pulse was 68, the temperature 97.6 F, weight 132, calculated ideal weight 150. The blood count was red cells, 3,030,000, hemoglobin, 70%, color index, 1.2. The white and differential counts were normal (Table I, case 5), and abnormal red cells were not found. The Wassermann was negative. The urine was normal. The gastric contents showed free HCL 37, total acidity 45, mucus and occult blood were absent. The basal metabolic rate was minus 35 per cent. After the administration of thyroxin 18 mg daily for a year the basal metabolic rate was minus 5, and all symptoms were relieved. Her blood count was red cells, 4,300,000, hemoglobin, 81%, color index 0.9. A continuation of treatment maintained her health at normal.

*Case No 18* (Table I) Miss B H, aged 50, who had a good family and personal history, began seven years before to complain of indigestion, which consisted of bloating, with gas and constipation. For relief of these symptoms the appendix was removed, but she was not benefitted. Later on she developed a bad taste in the mouth, weakness, and giddiness. A blood count showed an anemia, for which she took iron pills by mouth and sodium cacodylate by injection. This treatment she continued most of the time for the preceding five or six years. Many abscessed teeth were extracted. In spite of these measures she lost ground steadily, and became so weak that she spent much of her time in bed. When she was first seen

TABLE I THE BLOOD IN TWENTY-THREE CASES OF MYXEDEMA

Case No	Initials	Race	Sex	Age	Date	Basal Metabolic Rate	Red Blood Cells	Hemoglobin	Index Color	White Cells	Neutrophils	Lymphocytes	Large Mononuclear	Transitional	Eosinophils	Basophils	Abnormal Red Cells
1	NN	W	F	46	5 31 21	-40	3,140,000	40	0.6	7,300	69	31					Anisocytosis
2	THB	W	F	37	11 12 20	?	4,130,000	74	0.9	8,400	62	31	3	2	2		Poikilocytosis
3	AB	W	F	39	2 23 22	-23	3,008,000	70	1.2	6,400	70	26	4				None
4	BK	W	M	21	5 11 22	-30	3,650,000	73	1.0	6,200	50	44	2	3	1		None
5	AU	W	F	50	9 15 22	-35	3,030,000	70	1.2	7,200	58	36	1	3	2		None
6	FPH	W	M	48	7 7 23	-30	5,820,000	113	0.9	8,200	65	30	1	3		1	None
7	SHM	W	F	53	7 12 23	-17	3,700,000	70	0.9	6,200	58	34	4	3	1		None
8	NB	W	F	27	9 15 23	-36	4,592,000	80	0.9	5,960	67	27	4	1	1		None
9	FS	W	M	24	9 30 24	-36	4,910,000	81	0.9	6,000	65	32	2	1			None
10	NR	W	F	37	12 31 24	-31	5,380,000	95	0.9	8,000	61	28	7	3	1		None
11	JVJ	W	F	37	2 25 25	-20	4,840,000	96	1.0	8,400	56	38		5	1		None
12	MK	W	F	58	5 25 25	-27	4,576,000	75	0.8	9,400	73	25	2				None
13	CAE	W	F	34	8 2 27	-34	5,600,000	98	0.9	6,200	72	26		2			None
14	RB	W	F	52	7 6 27	-25	3,600,000	75	1.0	4,900	79	20		1			None
15	GW	W	M	53	8 19 27	-45	4,230,000	82	0.9	7,100	63	33		2	1	1	None
16	WAV	W	F	51	11 23 27	-23	2,750,000	50	0.9	2,000	73	20	4	2	1		None
17	WAH	W	F	53	6 23 27	-41	3,130,000	55	0.9	9,600	50	47	2	1			None
18	BH	W	F	50	7 19 27	-40	4,310,000	80	0.9	8,800	52	43	2		3		None
19	AL	W	F	45	11 1 27	-24	3,300,000	78	1.2	6,100	64	19	8	4	2	3	None
20	EFS	W	F	34	11 22 27	-28	3,950,000	85	1.1	6,750	65	33		2			None
21	AB	W	F	46	12 9 27	-39	3,580,000	68	1.0	6,800	50	48			2		None
22	NS	N	F	46	1 16 28	-20	4,200,000	81	0.9								None
23	LH	W	F	41	2 21 28	-27	3,660,000	71	1.0	6,200	59	37	2	2			None
							4,000,000	75	0.9	6,200	56	41	2		1		None
							4,375,000	73	0.8	5,050	75	16	4		5		None
							4,600,000	65	0.7								None
							3,450,000	75	1.1	7,950	54	32	10	2	2		None

July 19, 1927, the skin was dry, pale, and had a yellowish waxen look. Chronic follicular tonsilitis was present. The abdomen was considerably relaxed and was of the ptotic type. The heart rate was 60, the rhythm was normal. Blood pressure, systolic 104, diastolic 70. The temperature was 99 F, weight 135 pounds, calculated ideal weight 144 pounds. Urinalysis and Wassermann were negative. The blood count was red cells, 3,580,000, hemoglobin, 68%, color index, 0.9, leucocytes and differential count, normal. Gastric analysis, free HCL 0, and a total acidity that varied between 5 and 16. The basal metabolic rate was minus 40%.

Her treatment consisted of desiccated thyroid nine grains daily, and dilute hydrochloric acid minims twenty, and pepsin grains twenty after meals. After a few months of treatment her gastro-intestinal symptoms and weakness were greatly improved. October 17, 1927, the basal metabolic rate was plus 5. January 31, 1928, the blood count was red cells, 4,220,000, hemoglobin 81%, color index, 0.9.

*Case 15* G. W., a farmer, aged 53, was admitted to the John Sealy Hospital August 19, 1927, complaining of weakness, and swelling of the body. His father died at 52 of gastric cancer, and one sister had a goiter of unknown type. In the past his only illness of consequence was typhoid fever at 30 years of age. This left him with a chronic cholecystitis, which was drained surgically five years ago. The present illness actually began in 1919 when he had diarrhea, passing four or five thin offensive

stools daily. At that time he was a patient in the John Sealy Hospital, where a diagnosis of pernicious anemia was made. On June 25, 1919, the blood count was red cells, 2,790,000, hemoglobin, 78%, color index, 1.5, white cells, 4,800, neutrophils, 46%, lymphocytes, 49%, large mononuclears, 3%, transitionals, 1%, eosinophiles, 1%. The urine and Wassermann were negative. Achylia gastrica was present. He received during the summer of 1919, three blood transfusions totaling 2500 cc. Considerable improvement was made in his blood count, which rose after the transfusions to red cells, 4,280,000, hemoglobin, 90%, white and differential counts normal. However, he was greatly improved in health, but was unable to work. In 1926 he consulted a physician, in a neighboring city, who gave him another transfusion, but with only slight benefit. At the time of his last admission to the hospital, August 19, 1927, his complaint was weakness, abdominal discomfort and the passage of three or four loose stools per day.

The patient showed marked pallor of the skin and mucous membranes. The skin was dry and edematous. Over the legs the edema pitted on pressure, but did not do so over the rest of the body. The weight was 179 pounds, calculated ideal weight 178. During his stay in the hospital the temperature varied between 97 F and 100 F, and the pulse between 80 and 100. The blood pressure was systolic, 102, diastolic, 85. The blood count showed red cells, 3,130,000, hemoglobin, 55%, color index, 0.9, white cells, 9,600, neutrophils, 50%,

lymphocytes, 47%, large mononuclears, 2%; transitionals, 1%. Abnormal red cells were not observed. The urine was negative, and other evidences of renal impairment were lacking. Achylia gastrica was present. By the teleoroentgenogram, August 26, 1927, the transverse diameter of the heart at the apex was  $16\frac{1}{2}$  cm, the aortic arch 7 cm, transverse inside diameter of the chest 28 cm, which was an increase above normal of 5 cm over the cardiac measurement at the apex. The basal metabolic rate was minus 41.5%. Under full doses of desiccated thyroid his weight dropped to 150 pounds in twenty-one days, a loss of 29 pounds, which was due very largely to the removal of the edema. On October 19, 1927, less than two months after the treatment was begun, the teleoroentgenogram showed transverse diameter of the heart at the apex was 11 cm, aortic arch 6 cm, transverse inside diameter of chest 28 cm, a loss in width of the heart of  $5\frac{1}{2}$  cm, or a size that was within normal limits. The last observation of the patient on January 21, 1928, showed that his basal metabolic rate was minus 7%. The blood count was red cells 4,310,000, hemoglobin, 80%, color index, 0.9, white and differential counts, normal. The weight was 126 pounds. Symptomatically he was relieved, and felt strong enough to walk four or five miles daily.

#### COMMENT

The statement made in 1881 by Charcot (10), who is credited with being the first to observe that patients with myxedema might be "anemic to a high degree," is fully justified by

the findings in this series of myxedematous patients. Of especial interest are those myxedematous subjects who show a combination of anemia and achylia gastrica, because of the possibility of confusing the diagnosis with pernicious anemia. The normal red blood cell count and differential blood count together with an absence of abnormal red cells should serve to put one on guard.

In the present series of twenty-five cases of myxedema, achylia was found in four, or 25%, of sixteen cases in which the gastric contents were examined. The exact relationship between the hypothyroidism and the achylia is uncertain, but the fact that there has been a persistence of the achylia in all re-examined cases indicates that they are coincidental. Lusk (11), and others have reported the presence of both myxedema and pernicious anemia in the same individual, a possibility which should always be borne in mind. In very doubtful cases the effect of treatment may be necessary to complete the differential diagnosis. However, in the large majority of instances it is true that the anemia found in connection with cal myxedema is due to the low thyroid function, and it is relieved by the administration of thyroid substance. It is generally found in myxedema anemia that the blood count does not show such a high grade of anemia as the physical appearance of the patient suggests, which is doubtless due to the peculiar characteristics of the skin in myxedema.

The manner in which the anemia secondary to myxedema is produced seemed best explained on the basis

that there is a depression of function in the hematopoietic system by the hypothyroidism. This view is consistent with the belief that there is a diminished function of other tissues, and obviates the necessity of presuming that the thyroid gland elaborates a special hematopoietic hormone, as some have suggested.

### CONCLUSIONS

1 The blood findings in a series of twenty-three cases of myxedema have been presented.

2 In this series a secondary anemia occurred in 13 of the cases.

4 The anemia is due to the lowered content of thyroxin in the body acting upon the blood forming organs.

5 The blood changes in myxedema are concerned almost exclusively with the red blood cells and hemoglobin.

6 The leucocytes are usually normal in number, and the differential counts are inconsequential.

7 The administration of thyroid substances usually causes the anemia to disappear, while other treatment fails until the specific deficiency is corrected.

3 The similarity of hypothyroid anemia and pernicious anemia has been discussed.

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# Editorial

## JOHN HUNTER'S VIEWS ON CANCER

Hunter's conceptions of "cancer" are condensed within about a dozen pages in his *Lectures on the Principles of Surgery*. Nevertheless, within this small space are contained statements of facts that hold good today. This is particularly true of his views on the treatment and cure of cancer. The accuracy of his judgment is astonishing when we consider that it is based wholly upon the natural-history method of observation and deduction. That is, *all* that he knew of cancer was wholly clinical and from his clinical experiences he drew his conclusions. It was as if he mentally arranged his cases on a museum shelf, noting, comparing, classifying and cataloguing, and finally making his deductions. Of the cellular and histologic nature of cancer he, of course, had not the slightest conception. Of what lay behind the gross appearances he possessed very little knowledge, and his interpretations of what he saw when he cut into a cancer were purely hypothetical and for the most part incorrect, when viewed from the standpoint of modern pathology. There could, of course, be no exact science of Gross Pathology until gross morphology had a solid foundation of Cellular Pathology. But without this solid foundation Hunter probably went as far as it was possible for the

human mind to go in mere clinical observation and deduction. The conditions grouped by Hunter under the term cancer comprised many things of non-neoplastic nature, just as still happens in the case of purely clinical diagnoses of today, but naturally more frequently in Hunter's time. He, himself, recognized this. He says of cancer—"The diseases most commonly classed under this name are in appearance very different and probably are very different in their nature, they should not, therefore, be called by the same name. I would call that cancer which produces the following effects viz, a circumscribed tumefaction with much hardness, and a drawing-in of the skin over it, as if the cellular membrane underneath were destroyed, then a species of suppuration takes place in the center, and ulceration of the external surface. This is its most frequent appearance." How true is this description of the most common aspects of superficial carcinoma—the destructive infiltration and induration, the umbilication or retraction, and the central necrosis and ulceration! We are quite sure that Hunter made few mistakes in his clinical diagnoses of carcinoma when he applied such criteria as these. As to the location, he then goes on to say "It most frequently attacks the conglomerate glands, and first the female breast; also the uterus, the lips, the external

nose, the pancreas, and the pylorus, besides which the testicle is very subject to it, though that is not to be classed among the conglomerate glands. So that when I speak of cancer, I mean a peculiar disease in some of the above parts." As to the frequency of location in the organs enumerated we would still agree, with two exceptions, the pancreas and testicle. As Hunter mentions the pylorus after the pancreas it is very possible that he bases his opinion of pancreatic cancer on advanced stages of primary gastric cancer involving the pancreas. Such a secondary involvement of the pancreas is common enough in the late stages of pyloric cancer, and Hunter saw only late cases at autopsy. His inclusion of the testis in the list of the frequent sites of cancer is puzzling. Destructive diseases of the testis must have been more common in his time than in ours, and it is most probable that tuberculosis, gumma and suppurative infections of the organ made up the bulk of the testicular diseases regarded by him as cancer. Particularly in the case of tuberculosis of the testis involving the scrotum would his description of the external appearances apply. After his definition and mention of the most frequent sites of cancer he then goes on to enlarge upon the peculiar characteristics of cancer and to give its differential diagnosis from scrofula. "When small they probably cannot be distinguished, but as they increase, the distinction is more easy. If cancer, it will vary in appearance by becoming less circumscribed, not having so determined an outline, from the cellular membrane about it becoming

diseased, the skin will be less movable, the nipple more or less retracted, and the lymphatic glands going to the axilla will swell." What a concise and perfect description of the most important clinical differential facts this is! He then after giving the characteristics of scrofula goes on to say: "In cancer, the surrounding parts that are affected by continued sympathy also become cancerous near the skin, that is, all the parts become blended in one mass, but in scrofula, although the surrounding parts are in action, yet that action is not so scrofulous as the part itself, so that the skin will sometimes heal over the scrofulous tumor, as I have seen in the testicles when suppuration had taken place, by which I determined the disease was not cancerous."

Cancer is one of the first class of our first division of poisons, viz, that which only produces local effects, though it has been supposed to contaminate the constitution, which would be terrible indeed, as we have no specific nor even a palliative for it.

When a cancerous tumor has been removed often, the sore does not heal, or breaks out again. Sometimes it breaks out in another part of the body, which has been thought a proof of its arising from the constitution. This last circumstance as often arises where there has been one, it does not, therefore, depend on that circumstance as a cause. However, the operation having or not having been performed does not affect the argument, unless they could prove that cancer is an act of the constitution, and acts as a chain or concentration of the cancerous poison, and that by stopping this it must go some-

where else But the proportion of those who have it break out in two different parts of the body, compared with those who have it only in one, is about half what the latter bear to those who have not the disease at all, or about five hundred to one I never saw it in two different parts of the same person, but I have seen it in more than two distinct points of the same part It often arises in distinct points of the same breast, but seldom at the same period, and some of these may be so much in their infancy when the operation is performed as not to be observable, but afterwards increase and require a second operation

It is, therefore, best to extirpate the breast completely at once, to remove the whole complaint

A scirrhus or cancer appears to have three modes of contaminating 1st, by continued sympathy, which is common to other diseases, 2ndly, by remote sympathy, which is peculiar to itself, 3rdly, by contact, or communication of its matter to other parts by contamination I have called these consequent cancers, in opposition to the original" How much one would like to be able to explain to John Hunter's shade, if one should ever meet it in etherial wanderings, the knowledge we today possess of metastasis In reading John Hunter we meet with passages such as this when we can almost painfully feel the puzzled gropings and effort of his mind in the attempt to understand phenomena, which, at that stage of the development of human knowledge, could not be understood at all Hunter is fully convinced that cancer is a local disease, and he goes on to argue this point He asks

"Does cancer then produce any effect on the constitution? When it has existed a long time we find slight fever and hectic, but this is no more than the effect of all long-continued irritations, or sores which are not disposed to heal, but no peculiar effect is produced on the constitution" This is no more than the modern serological laboratory has been able to say "It has been said that cancers are produced by ill health as rheumatisms are, but this arises from the age of cancer being the age of such complaints, and being thus the predisposing cause of both, but not particularly of the cancerous disposition"

Hunter then compares the cure of cancer with that of venereal infection, concluding, as follows — "If we remove a cancer and no absorption will take place, the sore will heal and the constitution will not suffer, but then the *whole* must be removed

Otherwise it will return If removed and there has been absorption, the parts heal, though the consequent [*secondary*] cancer goes on, but if the whole cancerous parts are removed, the constitution is free

This shows that a cure is the consequence of a total removal of the parts, notwithstanding absorption has taken place, if all the diseased parts are removed" Such statements of fact are precisely the battle-cry of the propagandists for cancer-prevention of today "The only powers of contamination of this poison [cancer] are 1st, When it spreads from the center, thus producing a disposition to the disease in the surrounding parts, and an extravasation of interstitial matter; 2ndly, when the disease extends to dis-

tant parts, as when little tumors form under the skin at some distance, not in the line of absorbents, and 3rdly, when it produces the same disease in the absorbents and glands" The rate of growth of cancer is then described by Hunter, sometimes slow, sometimes rapid, sometimes accelerated by inflammation, operation, etc., but in general he regards the growth of cancer as slow and, therefore, the more dangerous. As to the cause of cancer, he considers the three predisposing causes to be "Age, parts and hereditary disposition, perhaps climate also has considerable effect, though not a predisposing cause. The cancerous age is from forty to sixty years in both sexes, though it may occur sooner or later in certain cases. The testicle, for instance, often becomes cancerous at twenty or thirty, but then not from the disposition of the parts alone, but from accident." As we can hardly believe that malignant teratoma of the testis was more common in Hunter's time than it is today, it is evident that the more frequent destructive disease of the testis in the young men of his time was either tuberculosis, or venereal disease. "Cancer has been supposed to be in young people's eyes [so-called malignant glioma, sarcoma or retinoblastoma], therefore, it is most probable that the breast is less subject to it at this age, and other parts are not so much confined to age in this disease. We often see tumors in the breast at thirty, and probably some of them are cancerous, although scrofula is more to be suspected. When cancer occurs in the breast of women under forty, it is *more rapid in its progress than when the patient*

*is older, and also more extensive* [confirmed in our time], so that the operation succeeds better in the latter on this account. However, we seldom find it in the very young or very old. Although of the two it is most frequent in the latter. When it occurs in the young, does it not show a very strong disposition for this disease, and, therefore, more danger, from a greater likelihood of its returning?" Hunter next discusses more in detail "*the parts most disposed to cancer* [his own italics], those peculiar to the sexes, as the breasts and uterus in women and the testicles [!] in men. Cancers are more frequent in women than in men, in the proportion of three to two, owing, perhaps, to the more frequent changes taking place in these parts in the former. It is that change which renders them unfit for conception and changes the whole system, which is particularly obnoxious. Thus, the three predisposing causes are 1st, a peculiar part, 2ndly, the age of the patient, and 3rdly, the peculiarities of the part at this age. The parts next in order of frequency, and which are common to both sexes, are the conglomerate glands about the lips, nose, throat, tongue, pancreas, stomach, especially the pylorus, intestines, especially the rectum. Besides these, we have it in the eyes and glans penis. The disease also appears in other parts of the body, but, as most other parts are similar in structure it does not attack one more than another. It sometimes falls on the bones from contamination, but on no one in particular." In his next paragraph, which is headed "*Whether Hereditary,*" he

goes on to say "Some suppose cancers to be hereditary; but this I can only admit according to my principles of hereditary right, that is, supposing a person to possess a strong disposition or susceptibility for a particular disease, the children may also, but I have not yet ascertained the generality of this fact. In many persons it would appear that some of the predisposing causes are sufficient to become the immediate ones, as when the diseased action takes place at a certain stated time, without any immediate cause." Could there be any more concise statement of the modern belief in the heredity of cancer susceptibility or predisposition, and its relationship to extrinsic causes? As to the effect of climate upon cancer, Hunter had only heard that they are very rare in the West Indies, and apparently not frequent in the Friendly Isles, in spite of the fighting contests held between women in which the breast is the chief point of attack, he, therefore, on the basis of such information thinks it is most probable that climate has some power, both in disposing to the disease and in preventing it. Following the discussion of the predisposing causes, Hunter describes the symptoms of cancer in detail, the majority of his statements made in regard to these are still accepted at the present time. He saw no local symptoms peculiar to cancer, they are only such as would arise from any injury to the part involved capable of producing the same degree of local injury, irritation and pain, which will vary in character and degree with the nature of the part involved, as, in the bladder, the

symptoms will resemble those of stone, in the rectum, purging and tenesmus, in the stomach, sickness and vomiting, within the skull, headache and coma. Cancer, he believed, "gives rise to no constitutional symptoms, except such as would arise in other diseases from the long continued wearing pain and perpetual discharge." Finally, as to his views as to treatment, here again his marked modernity shows itself. How far removed from quackery was John Hunter in all of his conceptions of treatment? This is the most remarkable thing about him, considering the age of quackery in which he lived. He would be modern even today, as far as the treatment of cancer is concerned, and no doubt would have raged violently and hotly denounced the cancer-cures of today, as he did that of Mr Plunkett, in his own day. Speaking of arsenic as a cancer cure, he says "Arsenic seems to have some power of this kind [curative] and its effects might be increased, by being used internally and externally, but its use is very dangerous, and I am afraid insufficient for the disease. This is a remedy which enters into the empirical nostrums which are in vogue for curing cancer, and among which Plunkett's holds the highest rank. But this is no new discovery, for Sennertus, who lived the Lord knows how long ago, mentions a Roderiguez and Flusius who obtained considerable fame and fortune by such a composition. I was desired to meet Mr Plunkett, to decide on the propriety of using his medicine in a particular case! I have no objection to meeting anyone; it was the young

one, the old one is dead, and might have died himself of a cancer for aught I know. I asked him what he intended to do with his medicine. He said, 'To cure the patient.' 'Let me know what you mean by that, do you mean to alter the diseased state of the parts?, or do you mean by your medicine to remove the parts diseased?' 'I mean to destroy them', he replied. 'Well then, that is nothing more than I or any other surgeon can do with less pain to the patient.' Poor Woollett the engraver died under one of these cancer-cures. he was under my care when this person took him in hand. He had been a life-guards man, I think, and had got a never-failing receipt. I continued to call on Woollett as a friend, and received great accounts of the good effects, upon hearing which, I said if the man would give me leave to watch regularly the appearance of the cancer, and see myself the good effects, and should be satisfied of its curing only that cancer (mind, not by destroying it) I would exert all my power to make him the richest man in the kingdom. But he would have nothing to do with me, and tortured poor Woollett for some time, till at last I heard the sound testicle was gone, and at length he died." Hunter sums up his views on the cure of cancer in the

following—"No cure has yet been found, for what I call *a cure is an alteration of the disposition and the effect of that disposition* [*editor's italics*], and not the destruction of the cancerous parts. But as we have no such medicine, we are often obliged to remove cancerous parts, which extirpation will often cure as well as we could by changing the disposition and action." Hunter then, for several pages, gives the technical details of the treatment of cancer, and every young surgeon should know these several pages by heart, and apply in his own work the knowledge of operation, recurrence and metastasis, re-operation, etc., that he will find there. He will profit much. On reading Hunter one's admiration and wonder grows by leaps and bounds. What a wonderful man—but not an agreeable one! But what a mind! What a pity Hunter came so soon, if he belonged to us, today, and did for modern medicine, based upon cellular pathology, what he did for the medicine of the 18th Century, where might our science not be advanced—to what heights? Even his unpleasant, rough, fighting, smashing honesty is needed today—we still have cancer-cure quackery to be treated as he disposed of Mr Plunkett, but we have become too gentle, or afraid—which!

## Abstracts

*The Influence of Environment on Rheumatic Infection in Childhood* By REGINALD MILLER (The Lancet, May 19, 1928, p 1005)

Is there any evidence that environment plays an important part in the production of juvenile rheumatism? Considered as a widespread endemic disease of England, juvenile rheumatism shows one outstanding feature. Namely, it is massed amongst the children of the poor, and practically absent from the children of the well-to-do. This class incidence is so clear that it is evident that we cannot hope to understand the large scale production of the disease until we know the explanation of it. Have we any direct evidence that the environment is the correct explanation of this class incidence? The Medical Council's Report into the incidence of rheumatism in poor-law residential schools offers conclusive evidence in this line. Four schools, housing about 1800 children, who all came from the poorer classes, were examined over a number of years. Left in their own homes it is impossible not to suppose that dozens of instances of rheumatism would have arisen amongst them, yet transferred to the residential schools they remain practically free of the infection. On this single piece of evidence alone we may confidently base the opinion that juvenile rheumatism is essentially an environmental disease. There are, of course, many other confirmatory proofs of this view. There are other possible explanations of the freedom from rheumatism enjoyed by the children of the richer classes, such as contagion, heredity, and diathesis. As to the two last named factors the evidence shows that they cannot be of great importance. The theory of contagion has no sort of support among clinical workers on the rheumatic problem. Further, spread by contagion will not explain the

class incidence of the disease, and is not in agreement with the modern bacteriological conception of rheumatic infection. If the last is true rheumatism must be grouped with such infections as appendicitis and lobar pneumonia, rather than with diseases due to imported organisms such as tuberculosis. Family cases of appendicitis and pneumonia occur synchronously or in close succession, but no one thinks that contagion accounts for the thousands of these cases that occur. To sum up, therefore, the general question of the influence of environment on juvenile rheumatism, we may regard this influence as so powerful that it is fair to regard the rheumatism of childhood as an environmental disease. This view is supported by the general trend of medical opinion in England. What are the environmental factors of importance in the production of juvenile rheumatism? Climatic and seasonal incidence show that a combination of damp and cold predisposes to the disease. Although poverty is a predisposing cause of immense importance, it is not merely poverty per se that is responsible, since the very poorest class shows a lower incidence than the class of the upper poor, the disease hits particularly the families of policemen, postmen, railwaymen and decent artisans. No other disease but dental caries shows quite the same class incidence as rheumatism. Rheumatism is a disease of city life rather than of rural, and of industrial towns rather than of residential towns. The part played by diet and general nutrition is not clear. Miller believes that damp dwellings play a very important part in the predisposition of children to the disease. Rheumatism maps show that the greatest number of cases come, not from the poorest streets, but from those close to canals and submerged streams. The middle floors of houses, which are as a rule the driest, provide the fewest cases. The relationship to poverty is apparently

chiefly a relationship to residence in damp dwellings. The greatest incidence of rheumatism is to be found among the poor who live in damp areas and in damp houses. Miller concludes that juvenile rheumatism must be regarded as an environmental disease. General lowering of the resistance is produced by such factors as poverty, urbanization and industrialization, the tendency to rheumatic infection is largely determined by living in damp rooms, exposure to wettings, chills, catarrhs, etc. Poverty and damp houses are two chief environmental factors. Altering the environment of children is sufficient to prevent the appearance of the infection amongst them.

*Acute Rheumatism in Childhood* By C. J. MCSWEENEY (The Lancet, May 12, 1928, p. 959)

The study of rheumatism occurring in the school-children of Cardiff, made by the Health Officers of that city in 1927, comes to somewhat different conclusions from those in the preceding abstract of Miller's study of the disease in London children. In Cardiff 214 rheumatic children were studied, 65 of these had rheumatic fever, 133 had rheumatic pains at some time or other, 129 had rheumatic carditis resulting in permanent valvular disease, 44 had rheumatic carditis which at the time of examination had not yet produced permanent valvular disease, 9 cases showed erythema nodosum and 7 cases showed arthritis. The summary of findings obtained by this study was as follows. No significant differences as to size of tonsils or frequency of sore-throats were found to exist when a series of observations on rheumatic children was compared with a series of observations on a similar group of non-rheumatic children. Chorea, permanent heart disease and other rheumatic manifestations were found to have developed in several cases after tonsillectomy had been performed. During the inquiry some slight evidence of the infectivity of rheumatism was found. Overcrowding did not seem to predispose to the onset of rheumatism, but 13 of the 14 rheumatic children found living under over-crowded conditions showed evidence of cardiac in-

volvement. The incidence of dampness in the houses of 201 rheumatic children was not significantly higher than in the houses of 108 non-rheumatic children. Ground-floor dampness was found to exist more frequently in the houses of rheumatics (which were, as a rule, older houses) than in those occupied by the controls but this did not seem to produce a tendency towards any particular type of rheumatic onset. A general dampness of the house was more often associated with the onset of rheumatic pains than other types of onset, but the differences were not significant. Dampness of houses, of whatever distribution, did not appear to predispose to the onset of chorea in preference to any type of onset. Living in damp houses did not predispose especially to rheumatic fever or to cardiac involvement. No close relation was found to exist between proximity to water and the development of rheumatism. (These Cardiff experiences are wholly contradictory to the findings of the Subcommittee of the British Medical Association which considers that the disease in industrial towns is essentially one of children living in damp rooms.)

*Dietetic Aspects of Rheumatism in Children*  
C. WILFRED VINING (Address at the Bath Conference on Rheumatic Diseases, May 11, 1928)

As the result of investigations carried out in Leeds Vining thinks that his views that the frank rheumatic child is a child suffering from toxic debility with added rheumatic infection have been confirmed. The "toxic debility" child presents the symptoms of nervous instability, limb pains, headache, listlessness and anemia. In Leeds 25 per cent of the child population from the social sphere in which rheumatism usually comes show these phenomena in greater or less degree. The "toxic debility" children exhibit certain intestinal symptoms associated with mucus and membranous material in the stools. The actually rheumatic children suffer the same way. Vining is impressed with the similarity of the symptoms shown by "toxic debility" children and those of McCarrison's monkeys and pigeons fed on diets insufficient in vitamin B. He believes



that a dietetic theory explains why rheumatism does not appear until 4 or 5 years of age—that is to say, the dietetic deficiency takes some years to break down the defense. The family incidence of both toxic debility and rheumatism may be easily explained by the family diet. In Leeds nothing was found to support the belief that dampness plays an important part in exciting the rheumatic infection to activity. Further, in Holland where enlarged tonsils and adenoids are extremely common among school children, chorea, joint rheumatism and cardiac are rare. Vining concluded that most children who develop clinical rheumatism have a previous defective health history for months or years, which is brought about by prolonged dietetic deficiency, either in vitamin B or in protein with excess of carbohydrate, or possibly by both these factors. If this view is correct, we shall not prevent rheumatism in children by concentrating on damp houses and the removal of tonsils and adenoids, but rather by the provision of a well-balanced diet from infancy onwards. He would not rule out the possible effect of damp houses nor deny that the tonsils may be the portal of entry, but he would maintain that an exclusive throat etiology is not warranted by the evidence at our disposal.

*Endocrine Factor in Rheumatism* W. LANGDON BROWN (Bath Congress on Rheumatic Diseases, May 11, 1928)

In dealing with the endocrine factor in rheumatism Brown thinks we may confine our attention to the ovaries and thyroid, the latter especially. He agreed with the pioneer Hertoghe that it was most important to look for evidences of hypothyroidism. Thyroid instability is the important thing, and it is possible also that spurts of hyperthyroidism on a background of hypothyroidism might be present in some cases. Lack of iodine is a feature in both, and iodine is useful both for goiter and rheumatism. Tonsillar sepsis may often be associated with thyroid derangement. It is possible that studies on the blood-sugar in rheumatism may throw some light on the endocrine factor. Insulin might be useful for rheumatic hyperglycemia. Thyroid inadequacy

may be the inherited factor in rheumatism, and at puberty and at the menopause the ovaries might act through the thyroid. Nevertheless, the thyroid and the tonsils are not the whole story in rheumatism—they are only factors. As far as endocrine factors are concerned the thyroid is the chief one in rheumatism and rheumatoid affections. There must be, however, no undue stressing of the endocrine and metabolic factors, the infective theory of the diseases takes first place.

*Effect of Ash of Liver on Blood Regeneration in Pernicious Anemia* By C. A. ELDEN and W. S. McCANN (Proc Soc. of Exper. Biol. and Med., June, 1928, p. 746)

Observations were made of the effect of ash of liver on blood regeneration in 3 cases of typical pernicious anemia. In two cases the administration of ash of liver resulted in the appearance of some of the preliminary phenomena of a remission, in particular an increase in the percentage of reticulocytes. In neither case did a true remission occur until Minot's liver extract 343 was given. The third patient with pernicious anemia received the soluble salts of the liver ash for a period of a week. There was no evidence of any activity of the bone-marrow observed, either in the total blood count and hemoglobin and leucocytes or in the percentage of reticulocytes. In the case of the two patients showing preliminary phenomena of remission, the beginning regeneration began to diminish as soon as the soluble salts of the liver ash were given, apparently the substance responsible for the beginning regeneration was lost or inactivated by dissolving the ash in hydrochloric acid, neutralizing with NaOH and evaporating the salts to dryness.

*Introduction of Iodized Oil into Respiratory Tract of Dog* W. E. SULLIVAN, K. F. FRIEDBACHFR, E. MCKINLEY (Proc Soc. of Exper. Biol. and Med., June, 1928, p. 751)

While the introduction of substances opaque to the X-ray was begun as early as 1905, it was not until the work of Sicard and Forrestier in 1921 that the practice

became general. They used a chemical combination of iodine and poppy-seed oil which is called lipiodol, and this is now in general use in diagnosis and in limited use in therapy. The question as to possible pathological changes in the lungs due to its use has never been wholly satisfactorily worked out experimentally. These investigators have carried out experiments along this line during the last two years. In one group the dogs were given 2 cc per kilo body weight and repeated when their urine became iodine free. This period varied from 23-67 days. Four dogs were used in this group. In the remaining dogs the treatment was empirical as is often the case in the clinic. Five small dogs averaging about 8 kilos were selected and the oil introduced at convenient periods. In the first group iodine tests of the urine were made regularly, as were also differential blood counts. While an occasional animal lost in weight their health on the whole was excellent. The greatest amount of oil given any one dog was 75 cc, the longest period that any dog was under observation was 205 days. At autopsy the lungs were studied in detail with the assistance of the Department of Pathology. Some attention was given to the other organs, especially the kidneys and spleen. The gross findings as a whole were negative. The microscopic examination in some cases showed a small amount of fibrosis and localized area of chronic passive congestion. This agrees with the recently reported observations by Pinkerton on the use of various oils in diagnosis, who found that one dose of iodized poppy-seed oil produced practically no reaction.

*Cardiovascular Findings in Women with Syphilis* By JOHN H. ARNETT (Amer Jour of Med Sc, July, 1928, p 65)

Two hundred and five female dispensary patients with tertiary syphilis, 25 with secondary syphilis and 78 controls were subjected to a uniform examination, including, where possible, an electrocardiogram and an orthodiagram. The following results were obtained. Cardiac enlargement as indicated

by a cardiothoracic ratio of 50 or over was present in a considerable number of the control group, as well as in both the primary and secondary syphilitic groups. No evidence was furnished for the belief that in the absence of definite evidences of cardiac impairment, syphilis *per se* may produce cardiac enlargement. On the contrary, unexplained high cardiothoracic ratios were found with approximately the same frequency in the controls as in the tertiary syphilitic group, and more rarely in the secondary syphilis group. In 3.2 per cent of the tertiary group the findings were deemed sufficient to warrant making the diagnosis of aortitis, and in 2 per cent aortic regurgitation. Arterial hypertension, both systolic and diastolic, was slightly more common in the tertiary syphilis group than in the controls. A somewhat greater frequency of arterial hypotension was found in the secondary syphilis than in either of the other two groups. Decided deviations from the normal electrocardiogram were shown more frequently in the tertiary syphilis group than in the controls, T-wave defects being the commonest abnormality noted. In several cases no other evidence of cardiac involvement could be found. The incidence of hypertension and cardiac enlargement increased rapidly with increasing age. Aortitis and aortic regurgitation were also more frequent in the older patients. Systolic murmurs were frequently noted both in the control and the syphilitic groups. Excluding 3 cases of aortitis from consideration, aortic systolic murmurs were no more frequent in the two syphilitic groups considered together than in the control group. Tachycardia at rest and two minutes after exercise was more common in both the secondary and tertiary syphilis groups than among the controls. Organic cardiovascular disease was not demonstrably present in any of the 25 secondary syphilis patients studied. No case of aneurism was found. Spirochetes were carefully searched for but not found in the myocardia of 2 cases of syphilis which came to autopsy during the early stage of the disease.

## Reviews

*Forensic Medicine* A Textbook for Students and Practitioners By SYDNEY SMITH, M D, (Edin), D P H, Regius Professor of Forensic Medicine, University of Edinburgh, Formerly Principal Medico-Legal Expert and Director of Medico-Legal Section Egyptian Government Service and Professor of Forensic Medicine, University of Egypt, Formerly Medical Officer of Health, Department of Public Health, New Zealand, and Examiner in Public Health to the University of New Zealand With Introduction by Prof Harvey Littlejohn, F R C S (Edin), F R S E, Late Professor of Forensic Medicine, University of Edinburgh Second Edition, 602 pages, 166 illustrations P Blakiston's Son and Co, Philadelphia, 1928 Price in cloth, \$8 00

The first edition of this work was published only three years ago, and the present one has been thoroughly revised. A number of new cases of general interest have been added, and the number of illustrations increased by about fifty, and it is hoped that the latter will greatly facilitate the study of the subject. The section dealing with the examination of fire-arms and projectiles has been enlarged and re-illustrated and part of the material dealing with this important subject has been transferred from the appendix to the general section on fire-arm wounds. The results of recent advances in many lines of work have been incorporated in this edition. Nearly one hundred pages additional material have been made necessary because of recent changes in Statutes bearing upon the subject of forensic medicine. This textbook has been written to meet the demand for a well-illustrated and concise manual of Forensic Medicine for students and practitioners. At the present time there exist very few textbooks in English upon this important field,

and most of these, such as Peterson and Haines and Draper's date back to the nineties. The American textbooks have not been revised to meet the present day requirements, and the physician in America who finds himself concerned in a medico-legal testimony is hard put to find helpful reading matter on the subject. The available textbooks he finds in the library accessible to him are almost certain to be out of date. It is also a fact that in medico-legal trials the average lawyer uses as authority only these old books. The great majority of the earlier writers on forensic medicine are dead, and the posthumous editions of any textbook are usually most unsatisfactory. A new textbook on forensic medicine by a living teacher of wide experience is therefore especially timely and welcome. Sydney Smith is eminently qualified to deal with this subject. There is only one path to the mastery of Forensic Medicine, and that is an extensive practical experience acquired by a daily whole-time application and study of the medical problems which are presented by the crimes of a large community. Sydney Smith has had a unique experience in Cairo where the crimes of East and West meet in the large and cosmopolitan population of that city, which has been called the most wicked of the world. One has only to visit Cairo in order to recognize that the wealth of medico-legal work there exceeds that of any European center. In the utilization of this material Sydney Smith has developed an Institute in this branch of medicine similar to those of Vienna and Berlin, and his Institute has become the center of a wide area outside of Egypt, including the Sudan and Palestine. The author has used his extensive experience as the foundation material of this book, and his views and conclusions based upon this constitute a valuable con-

tribution to the literature of forensic medicine. He has amplified the results of his own personal experience with an analytical survey of the world's literature bearing upon the individual subjects treated, so that the volume is not simply a recital of personal experiences, but embraces a wide survey of our knowledge along this line. The treatment of these subjects is well-organized, the style is simple, concise and clear, and the illustrations add valuable information. The size of the book is convenient for the uses of the student, and the medical student will find this volume of very great help in organizing his knowledge of legal medicine.

1 *Textbook of Medicine*. By American Authors. Edited by RUSSELL L. CECIL, A.B., M.D., Assistant Professor of Clinical Medicine in Cornell University, Assistant Visiting Physician to Bellevue Hospital, New York City, Associated Editor for Diseases of the Nervous System, FOSTER KENNEDEY, M.D., F.R.S.E., Professor of Neurology in Cornell University, Head of Neurological Department, Bellevue Hospital, New York City. Octavo of 1,500 pages, illustrated. W. B. Saunders Company, Philadelphia and London, 1927. Price in cloth, \$9.00.

There are 130 contributors to the make-up of this textbook on Medicine. Most of these contributors are teachers of medicine in University Medical Schools, and the list contains many well-known names among the older internists of this country, and a goodly sprinkling of the younger generation. The rapid growth of medical science during the last few years has made it almost impossible for a single individual to master the entire field. Specialism has necessarily split up the field of internal medicine into cardiologists, gastro-enterologists, specialists in diseases of the chest, kidneys, etc., and it requires a life-time to develop each of these special fields in a thorough way. The editor has compiled a textbook of medicine in which each disease, or group of diseases, would be discussed by a writer particularly interested in that subject, and

who is a student or investigator of the subject upon which he has written. This would undoubtedly have read much better and would have achieved very much better results if instead it had been "by a writer having expert knowledge of the given subject." This would have meant then that the contributors would have been composed of men having had much experience in the given line, and qualified to speak as experts, and, therefore, of necessity would have been on an average much older men than the list of contributors shows. That would be an ideal textbook of medicine, as far as this plan of individual contributors is concerned. In the first place it would be difficult in this country to get experts of this type to contribute to a textbook, such a plan was possible in the Germany of twenty years ago and still possible there in a lesser degree of efficiency and successful attainment. In this country it is practically impossible to create a thoroughly successful book on this plan, because so many of the subjects will be turned over to investigators in a given line who have no broad knowledge of the field they are working in, but are concerned only with their own personal investigations. The result is an article or chapter written with a personal bias, which may, after all, be a wholly mistaken one. Take, for instance, the subject of Yellow Fever, assigned to Noguchi and written by him wholly from the standpoint of the organism *Leptospira icteroides* as the cause of this disease. According to Agramonte and other yellow fever experts, there is not the slightest evidence that yellow fever is actually caused by this organism, and all through the world there are various investigators holding that this organism is identical with *L. icterohemorrhagiae*. From the standpoint of these workers, then, and those who have followed this work, this chapter on Yellow Fever is incorrect and misleading. This is not the only example of such "expert" contribution in this volume. In a textbook which is intended to be the final sources of knowledge on the given subject it would be much safer to have the articles written by men of largest clinical experi-

ence and knowledge than by experimental investigators in an individual line, who are more or less biased in their views, and lack the broader perspective necessary to a textbook. This criticism does not by any means apply to all of the articles in Cecil's textbook. Some of them are based on the broadest foundations and represent the subject from all necessary angles in a scientific manner. The conciseness of treatment and the condensation of material makes this textbook a popular one for students, and because of this it is the more unfortunate that many of its chapters are not more scientific and less narrowly personal. Medical knowledge is not yet in such an advanced state that every subject can be treated in a dogmatic manner, arguments on both sides must still be heard. It is difficult to do that today in the confines of a single volume, and perhaps there should be no attempt to do this, as the results, as shown in this volume, are not wholly satisfactory. There is too great an unevenness in the individual sections. In spite of its many excellencies this textbook is a glorified manual or handbook, appealing to students for its conciseness and brevity, but in too many spots not scientifically accurate.

*Recent Advances in Hematology* By A. PINEY, M.D., Ch.B. (Birm.), M.R.C.P. (Lond.) Research Pathologist, Cancer Hospital, London, late Director of the Charing Cross Hospital Institute of Pathology, London. Sometime Lecturer in Pathological Histology in the University of Birmingham. Second Edition. 318 pages, 4 colored plates and 18 figures. P. Blakiston's Son and Co., Philadelphia, 1928. Price in cloth, \$3.00.

A new edition of this little book was required in less than a year from the time of its first appearance. The author states in the preface to this edition that a number of additions will be found in every chapter and that the section on "The Spleen in Various Infections" is entirely new. He has tried, whenever possible, to make use of the criticisms of the first edition, but in some cases states that he has followed his

own views impetuously. He has aimed to include only purely morphological considerations, and not to include serology or immunology. He has intentionally ignored the subject of hemoglobin, as the recent advances in our knowledge of this subject are mainly biochemical and outside the scope of this book. To the American reader this book seems somewhat behind the times, particularly in the discussions on pernicious anemia, the neoplastic theory of Hodgkin's and the lymphoblastomas, etc. The word reticulocyte does not appear in the index, and the regenerative changes in the blood under liver diet in pernicious anemia are not mentioned. Ayerza's disease is not discussed, and there are numerous other omissions that come under the head of hematology. There are few new essentials in the material of this book differing from that of the first edition.

*Cardiac Arrhythmias. Clinical Features and Mechanism of the Irregular Heart* By IRVING R. ROTHE, M.D., Assistant in Medicine, Chief, Children's Cardiac Clinic, Mt. Sinai Hospital, Instructor in Post-Graduate Studies on Diseases of the Circulatory System Conducted by Columbia University at Mt. Sinai Hospital, N. Y. Introduction by Emanuel Libman, M.D., Clinical Professor of Medicine, Columbia University. 210 pages, 80 illustrations and 5 tables. Paul B. Hoeber, Inc., New York, 1928. Price in cloth, \$7.50.

The author has aimed in this volume to present in simple diagrammatic form the mechanism of the various types of cardiac irregularity together with their clinical signs, such as electrical manifestations, heart sounds and the arterial and venous pulses. The diagrams are drawn to scale in order that the various components of the extracardiac manifestations of the heart-beat may be correlated with one another and with the corresponding phases of the intrinsic cardiac mechanisms in any given arrhythmia. The attempt is made to simplify by aid of diagrams the understanding of that intrinsic disturbance in the cardiac

mechanisms known as "circus movement" which is accepted today as the underlying disturbance of rhythm in clinical auricular flutter and fibrillation. Text matter has been reduced to a minimum! it is a simple, clear text sufficient to make the mechanism and significance of the arrhythmias more easily understandable by the uninitiated. The diagrammatic representations of the mechanism of auricular flutter and fibrillation are original and striking. The first part of the book deals with normal anatomical and physiologic facts and phenomena. The second part deals with the arrhythmias exclusively. Clinical signs and symptoms are stressed throughout the volume. The author hopes that his book will awaken a wider interest in the bedside study of the irregular heart. It should be of great value to the general clinician in its presentation of the elements of graphic studies in the arrhythmias and the emphasis of their clinical features. The volume is handsomely printed, and the illustrations beautifully reproduced. To any one who does not feel sure of his understanding of the mechanism of the heart beat this book can be warmly recommended.

*Special Cytology: The Form and Functions of the Cell in Health and Disease*. A Textbook for Students of Biology and Medicine. Edited by EDMUND V. COWDRY. 2 volumes large octavo, 1,376 pages, 693 illustrations. Paul B. Hoeber, Inc., New York, 1928. Bound in waterproof sturdite, \$20.00.

This is a composite work to which some 33 writers have contributed sections along lines of cytology in which they have been personally more or less interested. The different kinds of cells which make up the human body—blood cells, nerve cells, gland cells, etc.—are treated individually in the separate sections. These contributors are chiefly anatomists. The book is to be regarded as supplementary to an earlier volume called "General Cytology" published by the University of Chicago Press in 1924, and now in its second printing. In that volume the fundamental principles of architecture and activity which cells of different kinds

possess in common were discussed by a group of workers chiefly recruited from the biological sciences, the purpose of this book is to present a detailed statement of the types of cells which make up the body, and which serve different functions, including both physiologic and pathologic conditions. These conditions as they appear in the adult are stressed, very little embryology is given. Known facts are given, and the probable explanations, and suggestions as to the possible line of advance. Methods of technique are treated only superficially, as it is proposed to publish a cooperative book on "Cytological Technique." Leading references to the literature are cited at the end of each section. The individual writers have at their own discretion utilized the literature at their own valuation, and instead of a mechanical review based upon abstracts of each research that has appeared on a given subject we see the literature through a personal selection and interpretation of the compiler rather than of the original author. Although the title page includes the form and functions of the cell in disease as well as in health, pathologic cytology is really given but little attention. The volume is essentially histologic, and the pathologic descriptions and interpretations very incomplete and inadequate. The articles, however, are very uneven in this respect. The chief value of the book is its encyclopedic collection and arrangement of the chief facts known concerning the cells of the various tissues and organs included in this treatment. To such an assemblage of cytological information it will be convenient for the laboratory worker to turn when he needs to refresh his memory as to some cytological fact or investigation. Such a compilation should have been prepared without any possibility of personal bias as to cytological conceptions, but in several places such personal views seem to appear. The book is well printed, but the reproductions of the illustrations are very uneven, due, no doubt, to the difference in style and quality of the originals. In spite of certain imperfections the two volumes will be indispensable to the working laboratory library.

## College News Notes

Dr Samuel S Berger (Fellow), Cleveland, Ohio, is now Internist in Charge of the Medical Service of Mt Sinai Hospital, Cleveland

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Dr L T LeWald (Fellow), Professor of Roentgenology, New York University, is scheduled to read a paper at the Second National Congress of Radiology at Stockholm on July 25, 1928. The subject of the paper is "Diaphragmatic Hernia Differentiation from Thoracic Stomach, Absence of the Left Half of the Diaphragm, and Eventration of the Diaphragm"

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Dr Carl V Vischer (Fellow), Philadelphia, Pa, presented a paper on "Ultra Violet Ray in the Treatment of Pulmonary Tuberculosis" with case reports, at the meeting of the National Society of Physical Therapeutics at Pittsburgh on June 21

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Dr G Harlan Wells (Fellow), Philadelphia, Pa, recently completed a successful year as President of the American Institute of Homeopathy. The annual meeting of the Institute was held at Pittsburg, Pa June 17-21, 1928

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Dr Karl Rothschild (Associate), Newark, N. J., recently addressed the staff of the Middlesex General Hospital, presenting reports with post-mortem notes on two cases, one of acute infectious myelitis (leptospirosis) and one of acute fatty atrophy of the liver, probably due to infection by virus

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Dr E Roland Snader, Jr (Fellow), Philadelphia, Pa, read a paper at the annual meeting of the American Institute of Homeopathy at Pittsburgh, Pa, entitled "Diagnosis of Renal Diabetes," with case reports

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Dr Carl V Vischer (Fellow), Philadelphia, Pa, was recently appointed Director of the Department of Physical Therapeutics of St Luke's Hospital of Philadelphia

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Dr Donald R Ferguson (Associate), Philadelphia, Pa, read a paper entitled "Clinical Aspect of Massive Collapse of the Lung," (illustrated) before the annual meeting of the American Institute of Homeopathy at Pittsburgh, Pa, on June 20

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Dr H M McClanahan (Fellow), Omaha, Nebr, is the author of a new book on "Pediatrics for the General Practitioner"

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Dr W G Gamble, Jr (Associate), Lecturer in Clinical Pathology, Medical College of South Carolina, Charleston, has been appointed as Instructor in Pathology also. Dr Gamble and wife attended the meeting of the American Medical Association at Minneapolis in June where he presented a paper entitled, "The Young Clinical Pathologist" dealing with the acute lack of Pathologists in this country, before the American Society of Clinical Pathologists. Mrs Gamble represented the South Carolina Auxiliary at the national meeting of the Auxiliary to the American Medical Association

Dr James Birney Guthrie (Fellow), New Orleans, La, is President of the Orleans Parish Medical Society

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Dr John B Youmans (Fellow) has been appointed Associate Professor of Medicine at Vanderbilt University School of Medicine, Nashville, Tenn

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Dr George H Whipple (Fellow), Rochester, N Y, was elected Vice-President, and Dr Howard T Karsner (Fellow), Cleveland, Ohio, was elected Secretary, of the American Association of Pathologists and Bacteriologists at their last annual meeting at Washington, D C The President of this Association, Dr Edward B Krumbhaar, Philadelphia, is also a Fellow of the American College of Physicians

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Under the presidency of Dr Lewellys F Barker (Fellow), Baltimore, Md, the Interstate Post Graduate Association of North America will meet at Atlanta, Ga, October 15-19

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Dr Henry O Colcomb (Associate), has recently been appointed Assistant in Neuropsychiatry at St Elizabeth's Hospital, Washington, D C Formerly, Dr Colcomb was located at National Soldiers Home, Va.

Dr Edwin C Ernst (Fellow), St Louis, Mo, is President of the Radiological Society of North America He was also recently elected to the Board of Chancellors of the American College of Radiology

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Dr Maximilian J Hubeny (Fellow), Chicago, Ill, just retired from the Presidency of the American College of Radiology Dr Hubeny is now the President Elect of the Radiological Society of North America, and was recently elected Chairman of the Section for Radiology of the American Medical Association

The American College of Radiology has a limited membership of one hundred Fellows, made up of men who have distinguished themselves in Radiology Dr Alfred L Gray (Fellow), Richmond, Va, is Presi-

dent, Dr Albert Soiland (Fellow), Los Angeles, Calif, is Executive Secretary, Dr B H Orndoff (Fellow), Chicago, Ill, is Treasurer, Dr I S Trostler (Fellow), Chicago, Ill, is Historian, Drs E C Ernst, St Louis, Mo, F A Groover, Washington, D C, G E Pfahler, Philadelphia, Pa, and R H Stevens, Detroit, Mich, are on the Board of Chancellors

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Dr I S Trostler (Fellow), Chicago, Ill, was made the recipient of a gold medal as a "token of service" at the meeting of the Radiological Society of North America in New Orleans last winter

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Dr Carl V Weller has been reelected Secretary of the American Society for Experimental Pathology For the ensuing year this carries with this office that of General Secretary of the Federation of American Societies for Experimental Biology In the Journal of the American Dental Association for June there appears an article by Dr Weller on Constitutional Factors in Periodontitis

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Dr Aaron E Parsonnet (Fellow), Newark, N J, has presented to The College Library the following reprints of work at the Newark Beth Israel Hospital, by himself and his associates during the present year

Abdominal Manifestations in Cardiovascular Disease

Electrocardiographic Control of Active Digitalization in Auricular Fibrillation

Quinidin Therapy, Uses and Contraindications in Auricular Fibrillation

Dr Thomas G Simonton (Associate), Pittsburgh, Pa, President-elect of the Medical Society of the State of Pennsylvania, addressed the Northampton County Medical Society, June 15, on "Pleurisy with Effusion and Referred Chest Pains"

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Dr Oscar W Bethea (Fellow), Professor of Clinical Medicine and Therapeutics, Tulane University School of Medicine, is author of a new book on Clinical Medicine, published by W B Saunders Company



Dr William A White (Fellow), Medical Superintendent of St Elizabeth's Hospital, Washington, D C, recently addressed the New England Society of Psychiatry at Providence on "Contribution of Psychiatry to the Problem of Crime"

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Dr Ada E Schweitzer (Fellow), Indianapolis, Ind, delivered the annual Chautauqua

lecture at the Winona Lake Chautauqua Child Health Week, July 9-13, entitled, "The Child and His World"

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Dr Henry Daspit (Fellow), New Orleans, La, has been appointed Dean of the Graduate School of Medicine, Tulane University of Louisiana, to take office at the end of the fiscal year, September 1928

# The Pathogenesis and Treatment of Dyspnea in the Light of Recent Experiments\*

By C S DANZER, M D, F A C P, *Instructor in Medicine, Columbia University, New York*

THE treatment of dyspnea is important not only because of its intensely disagreeable nature but because this symptom is indicative of a profound physiological disturbance in the supply of oxygen to the tissues. Furthermore in applying suitable therapeutic measures for the relief of this symptom, a favorable influence is incidentally exerted on certain very vital mechanisms.

For convenience we may divide the dyspneas into two general groups — 1—The spontaneous paroxysmal attacks, 2—The more insidious types brought on by effort or by the horizontal posture (orthopnea).

Under the first heading we wish to discuss three subgroups — *Cardiac Asthma* — *Bulbar Arteriosclerotic Dyspnea*—and *Broncho-spastic Dyspnea*. The second group comprises that variety most commonly seen in heart failure. It manifests itself as breathlessness on exertion and is followed later by orthopnea.

We hope to show that these forms of dyspnea can be separated, and that

each has its own mechanism and appropriate form of treatment.

*Cardiac Asthma* — This form of breathlessness, which sets in suddenly, usually when the individual is at rest, frequently awakening him from deep sleep, compels him to sit up in bed and pant for breath. The associated symptoms vary considerably in different cases. The pulse may be feeble and irregular or fairly strong and not very rapid. Râles (squeaking or bubbling) in the lungs may be present or absent, in some cases the attack may go on to pulmonary edema. Cough may be present and at times there is expectoration of a thin frothy sputum.

This wide variation in the character of the pulse and the degree of pulmonary congestion makes it possible that this symptom-complex is not an entity but embraces a variety of different conditions having a superficial resemblance.

Until quite recently the old Welch-Cohnheim theory of pulmonary edema, that of the left ventricular paralysis with strong right ventricular action, was offered as the explanation of cardiac asthma. The forcible pulse and the high blood pressure during

\*Read before the American College of Physicians at the Annual Clinical Week, March 8, 1928, New Orleans, La

the attack stand out as striking inconsistencies in this theory

The work of Eppinger (1) and his associates and Wassermann (2) shed new light on this problem. The former showed very clearly that during attacks of cardiac asthma the blood velocity is greatly increased. The retarding or brake mechanism normally resident in the capillaries is lost so that the blood surges with great rapidity from the arteries to the veins and is then thrust with great force into the right heart and lungs. The terrific rate of speed with which the blood flows through the capillary network scarcely permits the arterial blood to lose some of its oxygen. The body cells suffer and the nerve cells in the medulla respond by producing dyspnea. A convenient descriptive name for this condition might be *centripetal engorgement asthma*.

A study of the effects of different drugs on the blood velocity shows that those drugs which definitely retard blood velocity are most useful in checking an attack of cardiac asthma. Morphine and pituitrin have such an effect.

In view of the importance of the rapid blood-flow in the genesis of these attacks, I have attempted to check the excessive venous return-flow to the heart by a simple mechanical procedure. Four blood pressure cuffs are applied to the extremities and inflated to a point well above venous pressure. For convenience the diastolic pressure is taken as the measure of the constricting force to be applied around the extremities. This is applied for 10 or 12 minutes and then the cuffs are very gradually deflated. The lat-

ter fact is of great importance if we are to avoid overtaxing a strained heart by the gush of blood that would follow if the pressure were suddenly released. For this purpose we have constructed a simple apparatus called the "Venostat" which connects the four cuffs and permits the pressure in any or all of them to be regulated at will, by means of stop-cock arrangements.

When this is applied the blood pools in the four extremities thereby allowing the tissues of the limbs to receive their required oxygen quota, at the same time disembarassing the over-burdened heart and allowing it during the 10-minute period to restore to some extent its lost tonus. When one recalls the uninterrupted work of the heart during a lifetime, it seems possible that the reduction of the cardiac load for even as short a time as this may be effective. The relief that patients get from this procedure is very gratifying. In three or four minutes the breathing becomes less labored and slower, the patients exclaim that a weight has been lifted from the chest. Sonorous râles previously present diminish or even disappear for the time being, the right cardiac border recedes slightly and the patient loses his strained facial expression because of the relief of his dyspnea.

There seems to be a little obscurity concerning the manner by which a therapeutic procedure, which slows the blood velocity, acts in cardiac asthma. I should like to advance the following hypothesis. It is based on the correlation between the velocity and pressure in the veins and the cerebro-spinal pressure. The fact that

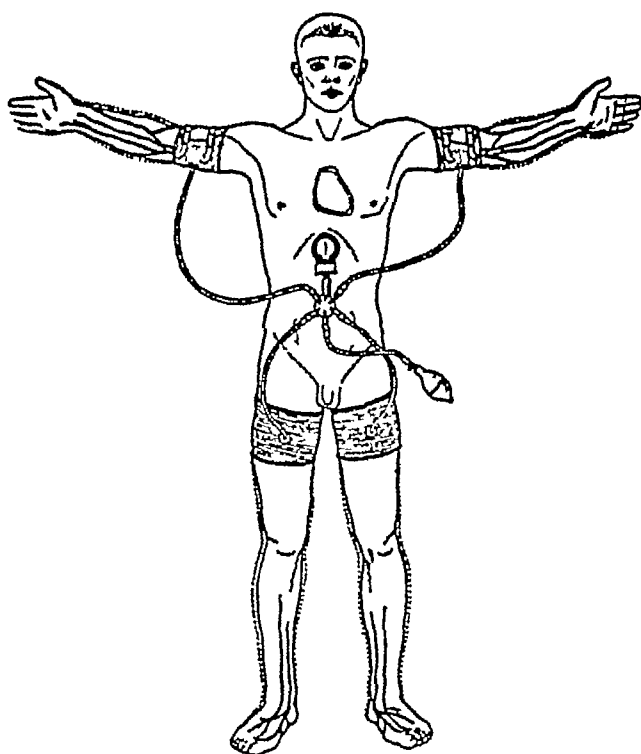


FIGURE 1—VENOSTAT

these attacks usually come during sleep (and the recent observation coming from Foster Kennedy's Clinic at Bellevue Hospital to the effect that intracranial pressure rises during sleep), has suggested the thought that a cranial hypertension may be a factor in the production of the attack. The flooding of the vena cava pre-

and cerebral venous sinuses must fall and likewise the cerebro-spinal pressure. One of the important coefficients in the production of the attack of cardiac asthma having been removed, the vicious cycle would be broken. That the spinal pressure actually falls after the venous compression in the extremities can be seen from the following—

*M.K. — Age—44 — Diagnosis — Tabes Dorsalis*

*Spinal Pressure*

Before	10 mm Hg	Venostasis has produced a drop in spinal pressure of 30%
Applied Venostat	7 "	
After removal of Venostat	12 "	

vents easy emptying of the cranial venous sinuses thereby causing a rise in pressure which is then transmitted to the cerebro-spinal canal.

By our mechanical method of withholding a volume of blood from the heart, the pressure in the vena cava

We have stated at the outset that cardiac asthma may be elicited by different mechanisms. A significant suggestion recently made by Wassermann is that such an attack may be an abortive or forme fruste of pulmonary edema. The early occurrence

of the tachycardia and the maintenance of an increased arterial blood pressure during the attack suggested the possibility of a reflex mechanism stimulating the sympathetic nervous system as the initial disturbance. If this hypothesis be correct an antagonistic reflex might inhibit the latter and so check the attack. The "Vagus Pressure" reflex, more correctly called the Carotid Sinus reflex by Hering (4) accomplished this very thing. The afferent arc of this reflex is the descending branch of the glosso-pharyn-

point to be compressed with the finger (Point 1 in Fig 2) corresponds to the bifurcation of the common carotid artery. The right side is usually more sensitive in eliciting this reaction than the left.

*Bulbar Arteriosclerotic Dyspnea*—As the study of the effect of venostasis was extended to other types of dyspneic paroxysms, another variety, clinically similar to cardiac asthma, was found, which was not benefited, even aggravated by this method.

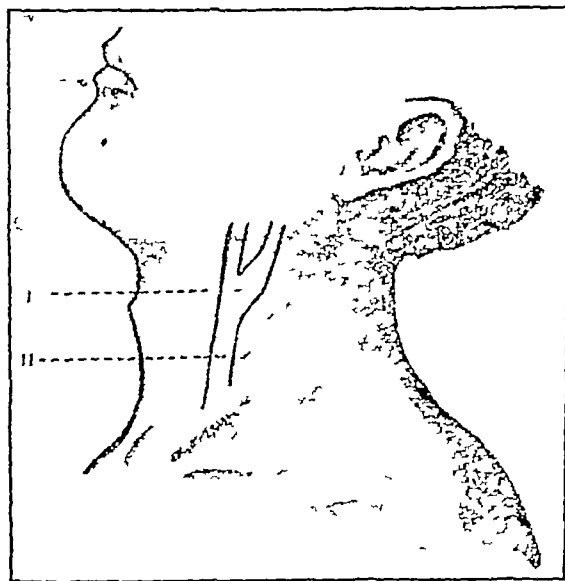


FIGURE 2—(After Hering)

geal nerve and the efferent part, the motor fibres of the vagi and the depressor vasomotor fibers.

The results of this procedure as reported by Wassermann are startling in that this severe clinical condition is checked very quickly. The compression must be made over a localized spot in the neck in order to elicit the vagus reflex. The illustration (Fig 2) is presented in order to clarify the

of treatment. Such patients show either the characteristic Cheyne-Stokes or the so-called undulating respiration (Wogende Atmung) in which periods of deep breathing alternate with those of shallow breathing. The patient feels breathless. There is often evidence of arteriosclerosis or hypertension. This condition has been called "Paroxysmal Hypertension Dyspnea" by Pal, "Renal

In other cases the breathing is deep, more frequent, though regular and only after the respiratory center is depressed by a hypodermic injection of morphine (gr  $\frac{1}{4}$ ) does it take on the Cheyne-Stokes character. With the onset of the latter the sensation of air hunger is much diminished.

The mechanism of Cheyne-Stokes breathing becomes clearer in the light of the following experiments —

Intravenous injections of 1 cc of adrenalin (0.2%) elicits this type of respiration in rabbits and cats (5).

Amyl nitrite (6) restores Cheyne-Stokes back to normal breathing. It seems possible that arteriospastic conditions of the medulla are responsible for this respiratory disorder.

It is corroborated by the observation of areas of softening in the medulla at post-mortem examinations of cases showing this type of breathing.

The point which we wish to emphasize is that the Cheyne-Stokes breathing may be masked by a hyperpneic reaction if the bulbar ischemia be very pronounced. In this case the excitation of the respiratory center may be removed by a hypodermic injection of morphine, thereby exposing the periodic form of respiration.

Since it appears to be an arteriospastic condition, the purin group of drugs seems indicated. Actually we have found that Euphyllin (a theophyllin derivative, which can be given intravenously) will check the Cheyne-Stokes breathing within a fraction of a minute.

For continuous medication Diuretin in 10 grain doses combined with 1-10th grain morphine sulphate t.i.d., and supported in some cases by

small doses of digitalis, has given very satisfactory results. The Diuretin and Euphyllin have a similar vasodilator effect.

*Broncho-Spastic Dyspnea* — The prototype of this form of breathing is seen in the attack of bronchial asthma. It is, however, by no means confined to the latter condition. Thus simple attacks of acute or chronic bronchitis may show it or it may be present during the course of a pneumonia.

To illustrate. A 59 year old man with a severe pneumonia with delirium, cyanosis, dyspnea, (orthopnea) and stupor was seen. It appeared to be a case of continuous dyspnea (to be described below) and venostasis was thought advisable. It was applied with marked improvement in his dyspnea, mental state and pulse. This state of well being was only temporary. After several days the dyspnea recurred. The venostat was again applied with great confidence but this time there was no improvement, the man was even made worse. On closer examination it was possible to explain these results. His dyspnea was expiratory in character, was associated with suppressed vesicular breath sounds such as occur in bronchial stenosis in which condition venostasis is ineffectual. This explains the failure to relieve the dyspnea.

Fortunately there are a number of pharmacological reactions which help to separate this form from other forms of dyspnea. I am referring to the favorable effects of epinephrin, ephedrin, atropine, large doses of caffeine or sodium iodide on this type of

dyspnea The presence of eosinophiles in the sputum also helps to recognize broncho-spastic dyspnea

I have on several occasions seen attacks of genuine cardiac asthma taken to be bronchial asthma because of the wheezing respiration, the presence of rhonchi and the associated emphysema These findings, however, may complicate cases of cardiac asthma They are not in themselves sufficiently characteristic to diagnose bronchial asthma The poor response to adrenalin and the beneficial effects from venostasis favor the diagnosis of cardiac asthma, thereby differentiating these two conditions at the same time

which the reduced vital capacity found in decompensated cardiacs were advanced to revive this theory That this inference is not correct may be seen from the respiratory tracings during decompensation and compensation

It can be seen that during heart failure the breathing is much deeper and each phase of respiration is quicker than during compensation This could hardly have been the case if the expansion of the lung had been reduced during decompensation

Peabody's work on vital capacity in cases of heart failure is correct The reduced vital capacity, however, is not be-



FIGURE 3 (After Hofbauer)

e—expiration  
i—inspiration

Decompensated  
Compensated after  
Digitalis

indicating the proper course of treatment This is a point of considerable practical value

#### *Continuous Dyspnea, Orthopnea and the Dyspnea Effort*

##### *A Physical Factor—*

For a long time Von Basch's theory of pulmonary rigidity consequent upon the engorgement of the interalveolar capillaries was the accepted one The expansile power of the lung was said to be reduced The recent studies of Peabody (7) in

cause the lungs cannot expand sufficiently It is due to another disturbed mechanism of respiration

If one looks at the profile of a person who is breathing deeply one can see that as the chest is lifted during inspiration, the abdominal wall (if in harmony with the descent of the diaphragm) moves forward In decompensated cardiacs there is frequently a paradoxical effect in that there is no inspiratory protrusion of the abdomen (See Fig 4) The abdominal wall protrudes instead of retracts dur-

ing expiration Wenkebach, Eppinger and Hofbauer (8) have shown this expiratory pump mechanism to be very important as an accessory factor in the circulation. Under this condition of reversed expiratory effect the return flow of blood from the lower extremities and liver is interfered with. The result is an edema of the legs, a congestion of the liver, and a reduction in vital capacity. The latter is due to the disturbance in expiration which makes it impossible to expel completely the air content of the lungs especially the reserve air

accompanying exertion, is the chemical reaction of the blood during work.

Our early results with the use of the venostat in treating cardiac asthma were so satisfactory that we attempted to treat other bedridden patients with orthopnea, cough and edema by this method. The patients were put on a limited fluid diet, no drugs were given and the veins in the extremities were compressed for 10 minutes at intervals of two hours. We were agreeably surprised to find that the edema lessened, the urine output

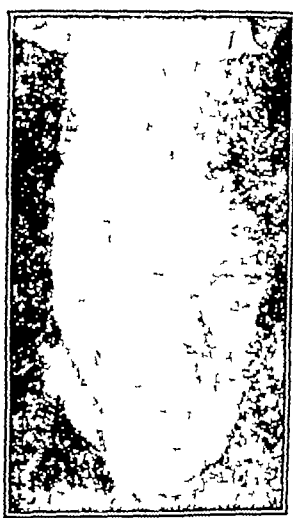


FIGURE 4—(After Hofbauer)

The therapeutic suggestion from these considerations is, to treat such cases by systematic breathing exercises so that the patient will properly synchronize his abdominal with his chest movements. By this means Hofbauer has achieved some brilliant results not only in relieving the dyspnea but also in reducing the edema.

#### *B Chemical Factor*

The next factor in the treatment of this type of dyspnea, especially that

increased and the dyspnea was favorably influenced.

These results were not very comprehensible at first, since it seemed that the venostatic method would be applicable only in conditions where the blood velocity was increased. Up to that time cardiac asthma was practically the only condition in which this was known to occur.

In 1927, however, Eppinger (9) published his studies on the dynamics



of circulatory failure and showed that the increased blood velocity in cardiac asthma was due to a relative increase in the acidity of the blood. This was the result of a  $\text{CO}_2$  retention. The existence of pulmonary complications (congestion or emphysema) was thought to interfere with the free diffusion of  $\text{CO}_2$  through the pulmonary capillaries. A reduction in the irritability of the respiratory centre during sleep and the diminished  $\text{CO}_2$  exhalation in shallow breathing were likewise considered operative in producing this effect.

He found that any condition which rendered the blood more acid, as the injection of acid into the veins of animals or allowing them to live in high concentrations of  $\text{CO}_2$ , caused cardiac enlargement due to an excessive venous return flow to the heart.

His next step was to show that in cases of cardiac decompensation there was a condition of latent acidosis. During exercise more lactic acid is produced in the blood than under normal conditions. It remains in the blood for an abnormally long time because the buffering mechanism in the blood and the tissues, by which this increase in lactic acid is neutralized, is defective. He found an increase in the lactic acid content of the blood from the radial artery in cases of heart failure.

Since acidosis is a factor in dyspnea it follows that the administration of alkali salts is indicated, as well as a diet tending towards the reduction in the acidity, namely, a lacto-vegetarian diet.

That benefits followed the use of lacto-vegetarian diet in dyspnea of cardiacs especially in the presence of arteriosclerosis was known for a long time. This concept has been ably championed by the great French clinician Huchard (10). Its mechanism at the time, however, was not clearly understood.

The last point that these researches clarified was the reason for marked dyspnea on exertion in certain functional diseases, e.g., "The Effort Syndrome" cases of the war period. These cases were frequently convalescents from the acute infectious diseases, influenza and pneumonia. It was striking to see their severe distress on mild exercise while patients with severe cardiovalvular defects carried on quite satisfactorily.

The explanation for this is given by the following experiments—If a dog or rabbit be placed in an atmosphere containing 10%  $\text{CO}_2$  he will develop an increased blood velocity and if allowed to remain in this atmosphere cardiac hypertrophy and enlargement will follow. The animals so treated, however, live on indefinitely because the buffering mechanism neutralizes the excess  $\text{CO}_2$  taken up by the blood. If the animal be given an artificial infection (staphylococcus or streptococcus) it will be killed by exposure in the  $\text{CO}_2$  in half an hour and present all the signs of severe acid poisoning (9). This shows that during the course of the infection the buffer mechanism had been impaired. This offers a chemical explanation for the clinical experience that infectious diseases frequently break down cardiac compensation. It also explains how

dyspnea on exertion may occur in cases without demonstrable heart disease in those whose buffering mechanism is defective, which was probably the case in the "Effort Syndrome" patients

Finally, these considerations indicate that we may apply certain com-

mon therapeutic procedures in cardiac asthma, heart failure, Effort Syndrome and acute infectious diseases in general — namely — alkalization by means of alkali salts and diet, and relieve the heart by checking the centripetal engorgement by the method of venostasis

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# Coronary Thrombosis\*

By J P ANDERSON, M D, *Cleveland Clinic, Cleveland, Ohio*

THAT coronary thrombosis presents a problem of differential diagnostic interest to the medical profession is evidenced by the many publications on the subject within recent years. A number of these articles have referred to the fact that coronary thrombosis may simulate gall-bladder disease. Nevertheless, the possibility that abdominal symptoms may be due to coronary thrombosis is not being sufficiently borne in mind. For that reason, while I propose to present a general summary of our present knowledge of this disease, I wish to call attention to this point, in illustration of which a selected group of cases will be presented.

From the large series of cases reported from various places at the present time, the incidence of the disease may be estimated. Christian (1) alone reports a series of 71 cases, and White (2) reports two series, one of 62 and one of 27 cases, covering periods of five years and of six months respectively.

Let us not be misled, however, into thinking of coronary thrombosis as a condition diagnosed only in recent years. Reviewing the literature of the disease, we find that in 1896 George

Dock (3) described four cases of coronary sclerosis and thrombosis which were verified by autopsies. One case apparently was due to rupture of an atheromatous abscess in the vessel wall, in the distal branches of which emboli of the substance were found.

De Lancey Rochester (4) reports having seen a case in 1893 in which the patient had frequent attacks of acute indigestion accompanied by severe epigastric pain requiring chloroform inhalations for relief. The final attack was terminated by rupture of the left ventricle.

Sir William Osler (5) reported a similar case in 1910. In his *Lumleian Lectures on Angina Pectoris* he presents the reports of some cases which were obviously coronary thrombosis. Osler recognized this differentiation, as he remarks of one case, "probably an attack associated with acute infarction of the ventricle as a pericardial friction was heard the next day." He also refers to several cases in which the patients had pain in the region of the liver accompanied by jaundice. One of these cases which was characterized by recurring attacks was diagnosed as gall stones, however, at operation no gall stones were found.

Much credit is due to Herrick (6) who in a report under the title of "Clinical Features of Sudden Obstruc-

\*Read before the American College of Physicians at the Annual Clinical Week, March 7, 1928, New Orleans, La.

tion of the Coronary Arteries" emphasized the facts that this condition can be justifiably diagnosed without necroscopic verification and that the condition does not by any means always cause death. Following Herrick's report came that of F. M. Smith (7) whose thorough experimental study showed the electrocardiographic changes and clinical course after ligation of the branches of the coronary arteries in dogs.

In 1926 Louis Hamann (8) presented a very comprehensive and complete summary of coronary occlusion. Faulkner, Marble, and White (9) have reviewed the histories of thirty cases of coronary occlusion, comparing the symptoms with those in thirty cases of cholelithiasis.

All the signs and symptoms which are reported by these authors have been seen in the cases of the disease in our Clinic. Not all the classical signs have occurred in each case, and without the history some of the cases could not have been diagnosed.

A previous history of angina or dyspnea on exertion is of great importance, but on the other hand, its absence is of no significance, as sometimes individuals who have always enjoyed the best of health are suddenly stricken without a moment's warning.

The classical onset of the disease is similar to an attack of angina pectoris but is more severe, being accompanied by excruciating pain which requires the administration of morphine in large and repeated doses and at times chloroform inhalation before relief can be obtained.

The following two examples will illustrate the fact that many of the

milder cases, as well as some which are more severe, may occur with little or no pain. In the first case the patient, while running for a car, developed a "shutting off" type of pain which made him slow down, however, he continued running, caught the car, and experienced an immediate cessation of pain upon being seated. Because this condition recurred on a similar occasion, the patient consulted a physician. Clinical findings showed an auricular fibrillation which has persisted ever since. The patient was only 34 years of age, had no rheumatic history, and had been accepted for life insurance shortly before. His heart rate did not respond to digitalis, and all electrocardiograms have shown an extremely low amplitude, so that we believe this condition can only have been caused by coronary thrombosis.

In the second case the patient, while driving home from his office, was seized with an intense dyspnea which caused him to lose the control of his car. He remembered everything except stopping his car, insisting that at no time did he experience any pain—simply an extreme shortness of breath. The electrocardiogram of this case showed inverted T's in the first and second leads.

The classical location of the pain in coronary thrombosis is the same as that in angina—in the substernal area, and it is of the "boring pressure" type. This may be the only site of the pain, or it may be referred to the left shoulder or arm.

We have also had examples of pain in more unusual locations. One man had sudden acute pain between the

shoulders and in the lower jaw, accompanied by slight fever. Osteopathic treatments proved useless, the pain increasing until morphine was required for relief. Even after all the teeth of the patient had been removed, the pain still persisted. This condition, however, gradually cleared up with recurrence of pain only when the patient overexerted, the pain being usually associated with some pain in the substernal area. The electrocardiographic tracing showed delayed ventricular conduction, with notched Q, R, S and inverted Ts in lead I. He eventually died in a prolonged attack of anginal pain. I believe this man had thrombosis of one of the smaller coronary branches at the onset of his trouble and died as a result of thrombosis in another artery. However, as there was no autopsy, the diagnosis could not be verified.

Another patient had attacks which radiated to the back, thereby causing intense pain over all the cervical and thoracic dorsal sensory nerves. The characteristic pain in the substernal area with no radiation, however, to either arm or to the abdomen was found in this patient who was only 43 years of age.

Another patient because of pain in the right shoulder consulted the Orthopedic Department. At the time of examination the shoulder was found to be normal, but after pain had been present in the chest for two days, fever began to develop, accompanied by a sense of impending disaster. Four days later the patient was forced to stop work and died suddenly that night.

### *Physical signs*

1 An anxious, worried expression, as if fearful of impending disaster

2 The skin becomes ashen in color, because of slight cyanosis underlying the paleness from shock, a condition which lasts long after the acute part of the attack is over

3 There is no characteristic posture although the patients often have to sit up and lean forward for easier breathing. They sometimes hold themselves as if transfixed

4 Wearn (10) has referred to a diffuse flushing early in the condition

5 The pulse is weak and may be alternating regular or irregular, slow or fast, whereas in simple angina there is seldom any change

6 The blood pressure shows a sudden drop in both systolic and diastolic pressures from a previous normal or markedly elevated level in contrast with that of angina. One case, however, showed the usual blood pressure reading of 185/120 mm up to the time of the last record a few hours before death

7 The temperature is normal or subnormal at first but rises about the end of the first day from 99° to 101° F, this elevation lasting from two to five days

8 The respiration may be normal, shallow, rapid or forced or Cheyne-Stokes in type

9 The precordial activity is feeble

10 The borders of the heart are nearly always widened because of dilatation, the left border often extending to the anterior axilla

11 The heart sounds are usually feeble, tic-tac or embryocardiac in character. A systolic murmur can be heard at the apex in about one half of the cases.

Phelps (11) has referred to a reduplication of the first apical sound as indicative of ventricular hypertrophy on the verge of failure. He states that within his knowledge all patients with this reduplication who have had major operations have died of progressive heart failure within one to three weeks after operation.

I thoroughly agree with him in regard to the risk of operative procedures but I believe the reduplication or "splitting" of the first sound is due to unequal contraction of the two ventricles, as I have found that such cases frequently show a bundle-branch block.

There are cases, however, where this does not seem to be the case, namely, those with acute hyperthyroidism in which a split first sound with gallop rhythm is fairly common. Likewise such cases do not show bundle-branch lesions and in operations they are not bad risks.

Pericardial-friction sounds are not always present but when found are almost pathognomonic. The absence of such sounds is explained in many cases by the facts that the infarcted area is frequently pyramidal with only the apex at the surface, that the infarct also may be so posterior that the friction is inaudible, and that friction sounds are evanescent and may be audible only for a few hours.

12 I shall refer to the rhythm under the electrocardiographic descriptions.

13 Pulmonary signs are nearly always present, the rapid edema and reduced resonance at the lung bases with the presence of numerous râles, sometimes suggesting pneumonia. I shall later refer to such a case. One of our cases showed such symptoms as hemoptysis and blood spitting, which are referred to in the literature.

14 Liver signs are often noted early, the marked congestion and distension causing great pain. I think this is readily understood if one recalls that many patients with mitral stenosis consult a doctor because of pain in the upper abdomen, the onset of which is never so sudden as in cases of coronary thrombosis.

15 Another heart-failure sign consists of gradually increasing edema, the findings depending on the time of examination.

In referring to heart failure signs, it should be understood that the coronary thrombosis may be in the left or right side of the heart and that the signs vary somewhat. With left-side damage, the lungs become affected quickly, other signs of failure being largely lacking, whereas with damage on the right side, the liver becomes engorged.

It must be remembered that the anterior descending ramus of the left coronary supplies part of the anterior surface of the right ventricle, so that it is possible to get right-side signs from a left coronary branch occlusion.

16 Signs of peripheral arteriosclerosis are not always present, though found in the majority of cases.

17 Anuria will be present during the period of markedly reduced blood

pressure According to Cushing this reduced pressure may be below 40 mm in dogs

In one of our cases anuria lasted for twenty-four hours but the blood pressure was below 50 mm about half the time

18 Embolic phenomena are apt to occur when pieces of the thrombus from the endocardial surface break loose Such symptoms were noted in only one of our cases, the embolus lodging in the right popliteal artery about thirty-six hours after the coronary occlusion had occurred

19 The chief laboratory sign is leucocytosis which appears shortly after the onset and corresponds largely with the temperature, the figures varying from 10,000 to 24,000

Urinalysis and blood chemistry findings depend largely on pre-existing conditions rather than on the present trouble, albumin and some casts being common Bile is not often found in the urine, a helpful diagnostic point in patients with referred abdominal pain It was found in only one of our cases and fortunately there was no suggestion of an abdominal lesion in this case

### *Electrocardiographic Signs*

The location of the infarcted area probably affects the electrocardiographic signs A few cases which clinically were very clear-cut cases including presence of a pericardial friction rub, have shown no electrocardiographic abnormality other than inversion of Ps in lead III, one case showing inversion also in lead II

Cardiac irregularities aside from extra systoles have been rather rare in our series No cases of complete or partial auriculoventricular block have occurred at any time during which patients have been under observation Only three cases of auricular fibrillation have been noted The greater number of cases have shown changes in the ventricular complexes In order to interpret these findings one must have a logical conception of the spread of excitation through the ventricles and the relation of this spread to the Q, R, S, T waves and intervals in the electrocardiogram

Assuming that the Bundle of His with its ramifications is responsible for the spread of the excitation waves, I think the simplest explanation is that electrical activity is continuous from the onset of the Q to the completion of the T, that Q is indicative of activation of the upper septal region, that R and S indicate the summation of activity in the two ventricles, that the S-T interval indicates the isoelectric period when the greater mass of the ventricles has been activated and that the Ts indicate a period of final activation of the musculature at the base of the ventricles toward the arterial orifices

An interruption of the usual spread by any overactive or inactive muscle will be shown by the electrocardiogram in the majority of cases If there is a lesion, however, high up in the bundle, there will probably be little or no change because of the double blood supply to the main bundle, whereas lesions lower down produce changes in the right or left bundle with bundle-

branch lesions or perhaps complete branched bundle block

Lesions in the peripheral ventricular wall will produce changes in the T's usually in the form of inversion in one, two or three leads. Very little attention has been paid to an inversion of the T waves in lead III unless associated with changes in lead II or I.

Smith (7) in his article on electrocardiographic studies following ligation of the coronaries in dogs, reports that none of the five animals surviving ligation of the right coronary artery showed appreciable aberration of T waves, while in every case of obstruction of the left coronary artery definite aberration was shown.

This observation may explain a similar condition in one of our cases which clinically was a very definite case and yet showed in the electrocardiogram no change except low amplitude. The patient was not seen, however, until six months after his accident, thus we cannot say that there was no change at the time.

The fact that coronary thrombosis simulates the symptoms of other diseases, such as gall-bladder conditions, presents a problem of differential diagnosis. Two striking examples of such simulation are reported by Levine and Trantor (12).

In the past four and one half years, we have made the diagnosis of coronary thrombosis 58 times, in 47 cases in men, in 11 in women. Twenty-seven patients are still living. Only two autopsy reports have been made. The question naturally arises as to the factors determining our diagnosis, seven of which may be briefly outlined —

1 History of sudden onset of pain of anginal nature but more severe, lasting for a period of hours or days and requiring opiates for relief.

2 Sudden onset of dyspnea which incapacitates the patient, as in the case already mentioned.

3 Onset of pain or persistent recurrence of pain while the patient has been perfectly quiet.

One patient had eighteen recurrences of pain in twenty-four hours, partially relieved by nitrites, and he died the following day. This is the case mentioned previously in which the patient had the pain referred to the cervical and thoracic segments.

4 Electrocardiographic findings of a complete or partial bundle branch block, if there has been a previous normal electrocardiographic tracing. A complete bundle branch block without anginal pain, in the absence of other explainable cause, has been considered as probably diagnostic of this thrombotic condition. Two cases of syphilis with bundle lesions have not been included here, as the lesions may have been due to gummata.

5 Slight changes in the Q, R, S complexes with inversion of T waves in two or more leads in the absence of medication affecting T waves, especially if this finding has been persistent in more than one examination. Altered T waves alone have not been considered sufficient diagnostic evidence, neither has any type of irregularity nor altered P waves.

The death of the patient during a prolonged anginal seizure has been found to be due to coronary thrombosis in one or two questionable cases.



6 The presence of a pericardial friction rub in a questionable case has been considered definitely confirmatory evidence, whether or not any electrocardiographic tracing was obtained

#### CASE REPORTS

*Case I* The patient was a man 71 years of age, a floor walker by profession, who entered the Clinic on June 2, 1927. His father died at the age of 76, of kidney trouble, his mother died at 55, of heart trouble. He had two brothers and two sisters, all of whom were living and well. In May, 1926, he had had nosebleed and had been told that he had high blood pressure.

At the time when we saw him, he had come to consult Dr. W. E. Lower, to find out whether or not he needed a gall-bladder operation. He had been quite well until three years before. At that time he had been about to take a street car when he had a premonition of illness and went into a drug store. There he suffered excruciating pain in the left lower quadrant of the abdomen, which quickly radiated to the right lower abdomen, then to the right upper abdomen, where it persisted. There was also pain in the substernal and clavicular areas.

The doctor who was called pronounced it gallstone colic and said he would have to be operated on at once. This the patient refused to permit until he had other consultation, and he was moved to his home. His family doctor pronounced the condition pleuropneumonia. He was sick for eight weeks and had to be kept under the influence of morphine during the first week. The patient said his fever was never so high as one would expect it to be in pneumonia.

Examination gave the following findings. A pale, slightly ashen appearance, arteries thickened++, retinal arteries+++, B.P. 210/110, P. 64. The heart was moderately enlarged, extending beyond the left nipple line and the action was grossly irregular because of extrasystoles. There were no signs of failure, no areas of tenderness in the abdomen. An electrocardiogram showed

a marked left ventricular preponderance, with inverted Ts in all leads and inverted Ps in lead III. There were numerous extrasystoles. The urine, blood counts and blood sugar were normal. Basal metabolic rate, estimated for scientific purposes,—1 per cent.

Our impression was that he was suffering from arteriosclerosis and that his former illness had been coronary thrombosis instead of pneumonia. He was kept at relative rest for two months and was given nitroglycerin. He then felt so much better that he was allowed to return to work, his blood pressure being 190/110. He remained at work for four months. Then one day he had to walk up seven flights of stairs and since that time he has had to stop work and has been unable to exert himself much without having an attack of substernal pain.

This case illustrates the fact that coronary thrombosis may be mistaken for either of two conditions. The first physician saw the patient at a time when he was having acute pain and tenderness in the right upper quadrant of the abdomen and he attributed it to gallstone colic, when in all probability it was due to engorgement of the liver with stretching of Glisson's capsule. When the second doctor saw him there must have been many râles in the lungs, which were considered to be due to pneumonia instead of the pulmonary edema.

In this case there was evidence of failure, first in the right side of the heart and later in the left side, and it is probable that there was thrombosis of the anterior descending ramus of the left coronary artery, which supplies the lower anterior wall of both the left and right ventricles.

*Case II* The patient was a man 68 years of age, who came to Dr. Crile on June 9, 1926 for cholecystectomy. His father died of cardiac trouble. The patient had had almost no previous illness except for mild rheumatism. In 1916 he had had one attack of some form of acute indigestion, and in August, 1923, two attacks of pain in the right subcostal area, partially relieved by elevating the leg and finally relieved by vomiting.

When he entered the Clinic the patient thought he was suffering from gall stones, as that diagnosis had been made previously. He had suffered from violent pain the night of December 12, 1925, with very severe pain in the right upper quadrant of the abdomen, attended by much vomiting. He was given morphin three times before he obtained relief, was unconscious for four days, and was very acutely ill for two weeks. Phlebitis developed in the right leg, and about a week later the same condition appeared in the other leg. This lasted about two or three weeks and was followed by bilateral pleurisy. It was the middle of February before the physician would risk moving him from the home of his relatives to his own home, which was only a few doors away, and he was confined to the house until the first of May. During the acute stage of his illness his temperature rose to  $99.5^{\circ}$  for several days, and remained at  $101^{\circ}$  for two days. B.P. 104/50 two weeks after the onset of the illness. No estimate had been recorded up to that time. There was no evidence of jaundice in the skin or urine. The pulse was usually good. White blood count, 22,000, polymorphonuclears, 89 per cent, three days after the onset of the illness. No precordial friction was noticed. The heart border was one inch beyond the nipple line.

At our examination, six months after the onset of the illness, his weight was 140 pounds—his average weight being 180—temperature  $98.2$ , pulse 79, blood pressure 104/78. An ashen color and arcus senilis were observed. The heart borders were 3 cm. and 10 cm. respectively, beyond the midsternal line. The sounds were very distant and of poor quality. There was a faint systolic murmur at the apex, the aortic second sound was slightly accentuated, there were no râles at the lung bases, the peripheral arteries were moderately thickened, the legs showed practically no edema.

The electrocardiographic tracing showed nothing abnormal except reduced amplitude, the waves were normal. A gastro-intestinal series was essentially normal. The duodenal bulb was slightly deformed but

there was no suggestion of an ulcer. A cholecystogram was made and no gall-bladder shadow could be seen 15, 19 or 23 hours after the ingestion of the dye. In the bromosulphthalein test no dye was recovered in 30 minutes.

This was considered to be a case of coronary thrombosis and the patient was allowed gradually to increase his exercise until he was going about considerably. He then returned to his home and has had biyearly examinations ever since. All electrocardiograms have shown normal waves. The patient was last heard from in February, 1928, and at that time he was still feeling well and was planning to make a trip to Europe this summer.

In this case the acute accident occurred while the patient was in another city. He was seen three times by a very competent consultant, and, so far as I am aware, coronary thrombosis was not considered, the condition being attributed to gallbladder disease with gallstone colic.

The cholecystogram gave evidence of disease of the gallbladder while the electrocardiograms have all shown normal tracings except for low amplitude. Nevertheless, I cannot conceive of any gallbladder condition which could produce a clinical course such as the one in this case—the very sudden onset with excruciating pain, requiring that the patient be kept under morphia for a week and unconscious for the first four days, the heart border one inch beyond the nipple line, with weak sounds and the blood pressure 104/50 about two weeks after the onset, no signs of jaundice in the skin, stools or urine at the time, the temperature rising to  $101^{\circ}$  and the white blood-cell count to 22,000. Add to this the fact that it was two months before his medical advisers would permit the patient to be moved a few doors to his own home and that it was six months before he set foot outside his house. Taking all these facts into consideration, it is very unlikely that gallbladder disease was solely responsible for his trouble. Both coronary thrombosis and cholecystitis may have been present, the former attacks being due to the gallbladder trouble and the latter attacks

to thrombosis. In any event, I think he owes his good condition to the fact that he had complete rest for six months and intensive rest for the next six months. No electrocardiograms were made until six months after the onset of the illness. The negative findings can be explained, I think, on the basis of Smith's work—he found that in no case did ligation of the right coronary artery cause inversion of the Ts—and of course it is quite possible to have an extensive lesion with no disturbance of the bundle conduction.

*Case III* The patient was a woman 55 years of age. Her husband has tabes but her Wassermann and Kahn tests have twice given normal results. She was first seen in May, 1925. Her chief complaint was of attacks of choking pain in the throat and of epigastric distress, which she has had since 1921. At that time she had a hypertension of 240.

The pain in the throat came upon exertion and was relieved by rest. When the pain was bad, it also came in the jaw and the patient felt as though her teeth were being pulled. The pain occurred under the sternum and radiated up the left side of the head and down each arm. The pain in the chest and neck was of the "clutching" type.

The examination of the heart gave essentially normal findings and the electrocardiographic tracing was normal. There was persistent tenderness in the region of the gallbladder. Plain gallbladder plates and plates made with barium showed no evidence of gallbladder disease, so we attributed the condition chiefly to angina.

In January, 1926, the patient's condition became so bad that she was admitted to the hospital. The attacks seemed definitely to be aggravated by food but there was no more tenderness in the abdomen than had been present all the time.

The patient was having pain more than half the time and insisted that something be done so I requested Dr C E Locke to perform a cervical sympathectomy. The superior middle and inferior cervical ganglia were removed *in toto* and this was followed by a typical Bernard-Horner syndrome. The patient's condition seemed somewhat

improved but she still had pain and the pain went also down the left arm. In September, 1926, while I was on my vacation, acute pain developed in her abdomen, radiating to the right subscapular area. This was different from any attack she had ever had before. Dr C L Hartsock had her enter the hospital, where a cholecystogram was made. This indicated a diseased condition of the gallbladder, so operation was performed by Dr T E Jones. Acute cholecystitis with a small abscess was found.

Following the operation the patient had relief from the angina for nearly a year. It recurred, however, with sudden pain, and an electrocardiogram made shortly afterwards showed inverted T waves in lead I. At the present time her electrocardiographic tracing is again normal. However, she still has anginal attacks, still has pain in the left arm, cannot walk more than 200 feet without having to stop because of a spasm, and still uses some nitroglycerin. In spite of all this she is taking care of a 15-room boarding house and does her own work except the scrubbing.

This case is chiefly one of angina but since, after an attack of severe pain, inverted Ts waves showed in the electrocardiogram, it is possible that a small vessel was occluded. It is a good example of a case in which two pathological conditions are present and of the confusion that may arise as the result. It is also an interesting fact that the anginal attacks and the pain referred down the left arm still recur after a complete left cervical sympathectomy.

*Case IV* This patient was a woman 62 years of age, who was seen on July 25, 1927.

Two nights before our examination, about ten o'clock in the evening, the patient was aware of pain through her chest which gradually grew worse until it seemed to run over her shoulders and down into her arms. It was equally severe in each arm. She thought that she must have taken cold. The pain must have lasted for at least several hours, for she thought of calling her daughter in the middle of the night, because she was suffering so severely. By morning it had entirely disappeared. She took a short walk during the day and felt

perfectly normal. When evening came, however, the pain returned so acutely that her daughter wanted to call a doctor. The patient did not think it necessary. She did not sleep all night and I was called at about 8:30 in the morning.

At the time of my visit the patient seemed to be having no discomfort. An examination of the heart revealed nothing. It did not seem much enlarged, there were no murmurs, no irregularity and no undue accentuations, and the sounds were clear. Percussion revealed no widening of the mediastinum. There was considerable tenderness in the region of the gallbladder on palpation.

This occurred after the patient in case III had been operated upon and while she was still free from anginal pain, so I considered the differential diagnosis between angina and coronary thrombosis or cholecystitis, which I might not have done otherwise. I gave the patient a hypodermic and asked her to stay strictly in bed. About 2:30 that afternoon I had a message that she was unconscious and she was dead when I reached her home. Autopsy revealed a ruptured heart, which appeared to be clear except for an area about 1.5 cm in diameter around the posterior descending branch of the left coronary. This portion was bright red and showed under the microscope fragmentation of the muscle fibres without any necrotic reaction. There was a small thrombosis in the sclerosed vessel. The gallbladder was normal.

I think this case should be classified as one of coronary sclerosis and dissecting rupture of the coronary artery, the rupture of the intima occurring on the first night and rupture of the remaining layers on the second afternoon, with a secondary rupture of the cardiac muscle.

*Case V* This patient was a physician, 52 years of age, who was first seen on November 25, 1921. The family history was negative for tuberculosis or heart trouble. His father died from nephritis and his mother from liver trouble. The patient had had tonsillitis in childhood and pneumonia in 1902. His left kidney had been removed five years before and there had been a

question of adenoma. He used no alcohol but smoked from two to four cigars a day.

The patient complained of a feeling of oppression and constriction over the precordium, which became very marked at times on exertion. He also had some trouble with gas on the stomach. One week before, after two heavy meals, he had had such severe pain in the epigastrium that at 4 A. M. he had to have a hypodermic of  $\frac{1}{4}$  gr of morphin and  $2\frac{1}{2}$  gr by mouth. The opiate caused vomiting. He had had a degree of temperature since that time. There was no shortness of breath.

On examination the chest expansion was found to be poor but equal on both sides, the heart was not enlarged, there were no murmurs, the aortic second sound was tympanic, the pulse was 72, B. P. 135/75, no arterial thickening, the abdomen showed a scar from the nephrectomy and there was some tenderness under the right costal margin.

The patient was not seen again until October 21, 1927, when Dr. Phillips saw him in consultation at his home.

On the preceding night he had been seized with a very severe pain in the epigastrium, with some nausea and vomiting, although this was not a marked feature. He at once became extremely pale and went into a condition of collapse. He was seen by a surgeon, who thought that he had a perforated gastric ulcer, but his condition was so serious that operation was not advised. He was also seen by Dr. Weller, who saw at once that the condition was cardiac in origin. The heart was considerably dilated to the left and to the right. The heart sounds were very faint. The blood pressure could not be estimated because it was so low. The heart was about 160. It was impossible to count the pulse, which was faintly perceptible. There were some changes at the base of the right lung and there was some enlargement of the liver. Morphine was given in moderate doses of  $\frac{1}{4}$  gr every four to six hours during the day, and the patient's condition became somewhat improved.

On the following morning the patient complained of very severe pain in the left

calf and in a very short time the left foot became cold. This was evidently due to an embolus of the popliteal artery. On examination the patient's color was found to be somewhat pale, though not so markedly as would be expected. The heart was considerably dilated to the left, the left border reaching to the anterior axillary line, and it was also slightly dilated to the right. The heart sounds were extremely faint, no murmurs could be made out but there was a suggestion of a pericardial friction rub in the left fourth interspace. Some crackles were heard at the base of the right lung. The liver was slightly enlarged. The left foot was cold and there was some thickening in the middle of the calf, evidently at the point of closure of the vessel. The patient died within an hour. A diagnosis of coronary thrombosis and embolus of the popliteal artery was made.

*Case VI* The patient was a man 51 years of age, who was referred to Dr Crile to be considered for thyroidectomy. His chief complaint was of nervousness with air hunger. His heart had been irregular since 1925. His tonsils had been removed in January, 1927. He had recently had two short attacks of pain in the chest and at times had had to sit up in a chair at night because of dyspnea. His weight was 153, his average weight being 195. Heart and pulse rate 84, irregular, with auricular fibrillation. There was no palpable fullness of the thyroid. The heart borders were 4 and 12.5 cm. beyond the midsternal line. There was a systolic murmur at the apex and in the aortic area. The arteries were thickened. There were a few basal crackles, the liver was scarcely palpable. An electrocardiogram showed auricular fibrillation with left preponderance and T's in the opposite direction and slurred. The first basal metabolism estimation gave +41, and a second, made three days later, +29 per cent. The charts showed a Cheyne-Stokes type of respiration. This case is chiefly one of coronary sclerosis, which has probably progressed to the point of occlusion of some small branches. Just why the basal metabolic rate should be so high I am not sure, but I believe it is associated

with the sclerosis rather than caused by hyperthyroidism. We have seen an increased basal rate in some cases of paralysis agitans.

*Case VII* The following case is reported to show that it is sometimes possible to rule out coronary thrombosis in making a differential diagnosis when there is a sudden attack of abdominal pain. In this case the pain was found to be caused by a gastric ulcer.

The patient was a man 65 years of age, who was sent to the hospital for a laparotomy because of sudden severe pain in the epigastrium. He had had one attack of vomiting without any blood. It was thought that he had a perforated gastric ulcer, but an examination was requested because of the possibility of coronary thrombosis. He had a previous history of gastric distress, his heart examination gave essentially negative results with no signs of failure, the electrocardiogram was normal and he had pain upon pressure and rigidity of the upper portion of the abdomen. The disturbance was reported to be not of cardiac origin and operation revealed a perforated ulcer at the pylorus.

*Case VIII* The patient was a woman 57 years of age, who had a Riedel's lobe of the liver extending to a point below the umbilicus in the lateral right rectus area, and in 1926 she had a sudden attack of severe pain in the upper right quadrant of the abdomen. She was seen by a physician who had not seen her before and he reported that she had a greatly distended, acutely diseased gall-bladder. Operation was not performed because of her cardiac condition. It is possible that the patient had cholecystitis but it is also quite probable that the cardiac condition was responsible for the abdominal pain, for she is now having some anginal attacks.

*Case IX* In 1921, a man about 60 years of age was admitted to the Toronto General Hospital in a prostrated and stuporous condition which, it was felt, was most probably due to uremia or to diabetic coma.

A history of the case obtained from his son revealed that the patient had been in

good health. That night he had started to eat a tomato and had choked on the juice. He gave a violent choking cough and then gasped because of excruciating pain in the chest and almost immediately became so prostrated that he was stuporous. He was brought immediately to the hospital.

The blood pressure could not be obtained, the patient's breath was negative for uremic or acetone odors, and the bladder contained no urine. Blood chemistry studies made on the following day gave negative results and about 16 hours after admission the patient died very suddenly.

Dissecting aneurysm of the aorta with rupture was suggested as the cause for this man's pain and death, and an autopsy revealed a dissecting aneurysm starting about one half inch above the aortic valve and perforating into the pericardial cavity about one inch higher up.

The pain apparently came with the rupture of the internal layer and the stretching of the outer layers of the aorta. I think it quite possible that that is what causes the pain in cases of coronary thrombosis rather than the presence of the clot with ischemia of the muscle.

Singer (13) has found in animal experiments that the arteries can be blocked with lycopodium spores and the animal evince no sign of pain. He also found that he could strip off the adventitial layer of the artery and ligate it suddenly, without producing any pain, but that if he pricked the adventitial layer with a needle, the animal would evince pain. Dr. Crile informs me also that the thyroid arteries are abundantly supplied with nerves and the patients evince pain when they are injured. From these findings it would seem that the pain is due to irritation of the nerves.

A thrombus does not always form after rupture of a calcified area of the aorta, and it is quite possible that the same is true in cases of rupture in the

coronaries. The weakened wall may then become stretched with any sudden increase in the blood pressure such as that caused by exertion or excitement and relaxes with rest or following the administration of nitrites. Does this not seem a plausible explanation of the pain in angina?

The pain in coronary thrombosis is similar in character, location and radiation to that in angina, but it is usually more severe and much more prolonged, and it seems probable that the only difference is that in those cases in which thrombosis develops, a more extensive rupture of the vessel takes place with greater stretching. The pain is naturally more severe and prolonged, and it seems quite logical that nitrites should not relieve the pain in these cases, also it is quite conceivable that thrombosis may result from only a small internal fissure and be associated with very little pain.

It is impossible to know whether or not thrombosis will develop in a case in which an attack of moderately severe pain has occurred, but this possibility should always be considered, and the case should be treated as a case of thrombosis. The patient should have a long period of absolute rest in bed until it is felt that he is completely out of danger. We do not know how long it takes an ulcerated calcareous plaque to heal, but it is a wise policy to err on the side of safety and to allow a longer period than may, perhaps, be necessary.

How much of the abdominal pain is referred from the heart and how much is due to sudden engorgement

of the liver with stretching of Glisson's capsule is not certainly known, but, as I said above, patients with mitral stenosis quite frequently consult a physician because of abdominal pain and tenderness, and in those cases the failure is much less acute than in cases of thrombosis

### CONCLUSIONS

1 The precursor of coronary thrombosis is coronary sclerosis with calcareous plaque formation, that is followed by rupture of the plaque, escape of tissue fluid and subsequent thrombosis and cardiac infarction

2 It seems probable that the pain is caused by the stretching of the ves-

sel wall rather than by ischemia of the muscle

3 The abdominal pain seems to be partially associated with sudden distension of Glisson's capsule

4 A theory is offered for the etiology of angina pectoris—the superficial rupture of calcareous plaques without the escape of enough tissue fluid to produce thrombosis, but allowing a stretching of the artery wall

5 Cardiac rupture may occur shortly after the onset of the thrombosis from rupture of the artery, or later from rupture of the infarcted muscle

6 A great many patients survive the attack and recover to lead a fairly active life for many years

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## The Abuse of Digitalis\*

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THERE is no member of the pharmacopeia more fascinating and intriguing than digitalis. The history of this drug is almost a medical epic. Its botanical name, *Digitalis purpurea*, was given to it by Fuchsius in 1542 because of the resemblance of its flowers to a finger or thumb and because of its purple color. Boerhaave regarded digitalis as a poison but other writers held that it was one of the native plants of England which should be considered a medicine of considerable virtue.

To that sterling old English physician, William Withering, the world owes a tremendous debt for his careful scientific investigation and clinical study of this remedy. Withering undertook the study of foxglove because he was informed of a secret remedy by which an old woman of Shropshire was frequently able to cure patients with dropsy who could obtain no relief from the leading medical men of the day. He began to use this drug in 1775 and after a period of ten years experience with digitalis wrote his masterly book. This in itself

would indicate that he was not affected by "pruritus scribendi." He gives an account of 163 patients to whom he had given the drug and also published communications from other physicians who had used it. He states that he reported all patients to whom the drug was given, without selection, in order to prevent any unwarranted enthusiasm for this remedy. His case reports are concise, clear and graphic, and deal, strangely enough, almost exclusively with the diuretic effects of the drug and the disappearance of dropsy. While he observed the fact that digitalis slowed the pulse when given in large doses he did not associate this effect with any benefit the patient received, in fact he rather considered the slow pulse as a sign that the maximum dose of the drug had been given. The advice which he gave 143 years ago and which for many years was disregarded, is still sound "let the medicine be continued until it either acts on the kidneys, the stomach, the pulse or the bowels, let it be stopped upon the first appearance of any of these effects."

Could Withering observe today the enormous growth and prestige which

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this lusty infant has attained, I venture to say he would be amazed, and even perhaps somewhat apprehensive

In spite of Withering's scholarly and lucid presentation of the subject the virtue of digitalis was practically ignored for over a hundred years

Pratt after investigating this phase of digitalis and reviewing treatises on heart disease states that after going through Hope, Stokes, Latham and Walshe, as well as Austin Flint, found that they paid little or no attention to Withering's teachings and apparently did not know the great value of digitalis in cardiac failure

He remarks however, that "Sir James MacKenzie, working over 100 years later, was the first clinician to demonstrate conclusively the correctness of Withering's instructions regarding the administration of digitalis"

While we must admit that this drug was ignored for a long period of time when it could have been readily used in medical treatment the situation has now been completely reversed and we find digitalis being put to every conceivable use so that untoward effects are a common observation. In certain disturbances of cardiac function there is no other known drug which is quite as effective. In the treatment of the congestive type of heart failure digitalis remains paramount. We must keep in mind, however, that digitalis is not the sovereign remedy for all affections of the heart, that its field is strictly limited, and that if we would employ it successfully we must have a clear understanding of its limitations and of its narrow field of usefulness

Too often after satisfying ourselves that the patient's difficulty is due to a failing heart we fall back on digitalis to relieve the situation and neglect the other obvious measures which in many instances may be more effective than digitalis itself

We should keep in mind the fact that digitalis has no effect whatever in curtailing the incidence of heart disease. The etiologic factors which make for cardiac failure are, as a rule, uninfluenced by the administration of this drug

The acute infectious diseases such as rheumatic fever which have such a sinister habit of attacking the tissues of the heart are not influenced by this drug

Wolferth in discussing digitalis states "when dealing with a failing heart, we are not relieved of the responsibility for searching out rigorously the underlying causes of that failure and retracing the course of events so far as possible to the very beginnings of disease. It is not necessary to say that digitalis does not cure faulty habits of life nor infected gall bladders, nor does it materially influence the bad effects of these and like on the heart. Even when—as is too frequently the case—our therapeutic efforts are limited to the symptomatic treatment of heart failure, our attention should be directed first towards securing comfort, rest, satisfactory sleep, adequate functioning of the gastrointestinal tract, and whatever else may be done to ease the burden on the heart"

When we assign digitalis to its proper place in medicine its field of usefulness becomes considerably nar-

rowed. We do not become unreasonable and demand of this drug the impossible. It can never restore elasticity to sclerosed blood vessels, it will not increase the lumen of constricted coronary arteries, it will not replace damaged and fibrosed cardiac muscle, it will not curb the malign activity of bacteria which have lodged in endocardium or myocardium and which there produce inflammatory reaction.

Our ideas regarding the action of digitalis on the heart have been considerably changed in recent years. We have regarded digitalis as a "cardiac tonic," a stimulant to the heart enabling it to perform more work. There is good experimental evidence to show that digitalis decreases the work of the dog's heart and that the actual output of blood is diminished following full therapeutic dosage. Harrison and Leonard showed that the drug caused an average decrease of approximately 25 per cent in the cardiac output per minute of dogs which had been digitalized. They regard the action of digitalis on the heart as similar to that of morphine on the respiration. This conception of digitalis as a cardiac sedative is contrary to current opinion. There is evidence to show that in heart failure the venous pressure is increased and that the heart in diastole fills to a greater extent than it would normally. This results in an increased output of blood at each systole of the ventricles so that the heart is actually required to pump more blood than it would in a normal state. This phenomenon may explain in some measure at least the desire of patients with cardiac failure to be propped up in bed and to insist even

on sitting up straight or even leaning forward. In this position the heart puts out less blood at each systole and harm may come to the patient if the recumbent position is insisted upon. Furthermore the cardiac patient will not only assume the upright position but will even feel better, often, if he can get his feet out of bed and allow them to hang over the side. This seems to be the most comfortable position he can assume and patients with cardiac failure may even sleep in this position or when leaning forward on their arms. Digitalis by increasing the tonus of the heart muscle and diminishing the diastolic relaxation tends to break this vicious circle established by the failing circulation.

This evidence would establish several important contraindications to the use of digitalis. If digitalis diminishes the cardiac output its use is contraindicated wherever evidence of diminished cardiac output exists without evidence at the same time of lack of ventricular balance. Such conditions occur in surgical or traumatic shock and after prolonged anesthesia. Digitalis has been widely employed in such cases because of its supposed tonic action on the heart. There is evidence to indicate that the drug may be actually harmful in these conditions.

There is considerable difference of opinion as to the value of digitalis in pneumonia. The evidence is inconclusive at present and there are insufficient data available to definitely answer this question. White in reviewing the records of several hundred patients who had gone through the Boston Hospitals felt that there was

a slightly lessened mortality among patients who had received digitalis. However, his conclusion was that the data were insufficient on which to base a definite recommendation. Many of the cases were given digitalis as a last resort, others received only one or two doses of digitalis, while others received digitalis from the beginning of their pneumonia. This disease offers a particularly fertile field for further observation regarding the effects of digitalis. Leonard and Harrison from their experimental work feel that the drug has been incorrectly used in pneumonia. They believe that digitalis should be given early in the disease and in full therapeutic doses in order to decrease the cardiac output. They believe that digitalis is contraindicated in pneumonia when outstanding evidence of circulatory failure is present. They recommend that digitalis be used to prevent and not to combat circulatory failure in pneumonia.

During the past few months we have used digitalis on alternate cases of pneumonia admitted for hospital treatment. In a series of 20 cases of lobar pneumonia digitalis was given to ten and withheld from ten. These cases were admitted in various stages of pneumonia and the drug was used irrespective of the condition of the patient or the day of the disease but was begun in the alternate cases immediately upon admission. The mortality of the two groups varied very little, but for ethical and scientific reasons

continued in the hope that eventually a sufficiently large number of pneumonia cases will have been accumulated to justify some conclusion regarding this important problem. It would appear, however, that the practice of giving small doses of digitalis in the early stages of pneumonia in order that the heart may be more easily digitalized if the occasion should arise for this action, appears to be unjustified.

Digitalis effect can be secured within six hours even when the drug is given by mouth and there would appear to be no reason for continuing the small dosage during the early days of the disease. No demonstrable effect can be shown from small doses of digitalis.

The question frequently arises as to the value of digitalis in hyperthyroidism. In this condition the state of the heart frequently determines the outcome. While no one would attempt to control the tachycardia and the cardiac damage which results from long continued hyperactivity of the thyroid gland by the use of digitalis, nevertheless this drug is of considerable value in the preoperative treatment of the patient. Digitalis has been frequently maligned because it failed to control the tachycardia and eventual myocardial failure resulting from hyperthyroidism when the thyroid was overlooked as the primary cause of the cardiac failure. However, it is often invaluable in preparing the patient for thyroidectomy.

abuse it has received and may be the deciding factor in the patient's recovery following operation

Digitalis has also been employed as a preoperative measure for a host of different conditions. There appears to be no justification for the routine employment of digitalis in patients with normal hearts before operation. If, however, the patient has evidence of cardiac failure digitalis would be employed in exactly the same fashion as a preoperative measure as it would be in the treatment of cardiac failure without an operation looming up on the horizon.

In past years much confusion existed regarding the efficacy of digitalis in the various types of cardiac arrhythmia. Since the work of Mackenzie much of this confusion has been eliminated. Through the development of the polygraph Mackenzie was able to obtain graphic records of both auricular and ventricular activity and to clearly distinguish and define the various types of cardiac arrhythmia. Up to the time of the polygraph digitalis had been given rather indiscriminately in irregular heart action and the great variability in its result was attributed to differences in the potency of preparations rather than to various types of arrhythmia treated. The effect of digitalis is now well defined and little excuse exists for its abuse in the treatment of cardiac irregularities.

Auricular fibrillation with congestive failure offers perhaps the greatest field of usefulness for digitalis. Its peculiar effect in depressing the auriculo-ventricular conductive system and blocking auricular impulses which

bombard the ventricle and cause it to respond at a tremendous rate, results in slowing the ventricular rate and often restores the heart to a fair degree of compensation.

Arrhythmia due to extrasystoles is not in itself an indication for the use of digitalis. Unless there is evidence of associated cardiac failure digitalis as a rule has no effect in lessening extrasystoles.

In the treatment of auricular flutter digitalis is often very effective. Its peculiar action in converting flutter to fibrillation is well recognized and when this phenomenon occurs the drug should be promptly discontinued. If this is done, frequently the rhythm returns to normal.

In paroxysmal tachycardia digitalis is often used and as a rule has little value in cutting short the attack. However, if signs of cardiac failure develop in long continued paroxysms of tachycardia, digitalis can be used to advantage. There is little evidence that digitalis will suppress or avert attacks of paroxysmal tachycardia and its routine use in such conditions is not warranted on the evidence at hand.

In patients who show incomplete heart block digitalis is to be used with extreme caution. Its peculiar property of diminishing conductivity of the auriculoventricular bundle may convert incomplete to complete block with, at times, serious consequences. The advantage of routine electrocardiograms in detecting partial heart block requires no emphasis. If, however, the patient already has complete block and there is evidence of cardiac

failure, digitalis can be used without hesitation

Distressing attacks of Stokes-Adams syndrome due to temporary occurrence of complete block may sometimes be averted by converting incomplete block to complete block and maintaining it with digitalis

Before dismissing the cardiac arrhythmias it is well to keep in mind the fact that digitalis is capable of producing every known type of cardiac arrhythmia and in fact may produce types of arrhythmia that can be caused in no other way than by the administration of this drug. Some of the most bizarre electrocardiographic tracings showing every conceivable type of irregularity are produced by the administration of digitalis either in excessive doses or to individuals who are particularly susceptible to this drug. The occurrence of arrhythmia following the administration of digitalis calls for a careful investigation and may be the first indication of the toxic effect of the drug

When heart failure occurs without any abnormality of rhythm digitalis is still effective if given in adequate doses. While it may be particularly effective during the first or second attack of cardiac failure, not infrequently, with subsequent attacks its value is less and less marked. This is the natural phenomenon to expect and should not lead to the abuse of the drug. As the disease process becomes further advanced, as the coronary circulation becomes increasingly impaired, as the myocardial muscle becomes replaced by fibrous tissue, digitalis becomes less and less effective

in maintaining an efficient circulation and eventually is entirely ineffective

There is no more distressing picture than that of the patient slowly and painfully dying of congestive heart failure. The scene is familiar to all of us—the patient upright in bed, gasping for breath, using all the accessory muscles of respiration in order to compensate for a failing oxygen supply, cyanotic, with distended limbs and abdomen and frequently hydrothorax, unable to get a minute's rest or peace and looking forward with relief to the moment when his suffering will be ended by death. There comes a time in the final stages of every cardiac patient when digitalis fails to sustain the circulation. These patients may take days or even weeks to die. When this stage arrives morphine offers the patient the greatest solace, and digitalis even if pushed to the point of beginning toxic symptoms eventually loses its potency and must acknowledge defeat

We would do well to look forward and bear in mind this distressing end picture which faces our cardiac patients. While many of them succumb to intercurrent infections or are removed from the picture by contact with a swiftly moving automobile, a fair percentage reach this end stage. This fact should stimulate us to safeguard the heart by every possible means in the early stages of heart failure knowing full well that eventually digitalis will no longer perform this important task for us. The elimination of foci of infection, the regulation of the patient's hygiene, the careful supervision of the dietary, the

regulation of the hours of work, sleep and rest, are measures which are equally if not more important than the adequate administration of digitalis

In valvular heart disease digitalis is often abused. Not infrequently we see following the diagnosis of a valvular lesion, a prescription for some form of digitalis. Valvular heart disease itself is not an indication for the use of this drug. When heart failure occurs and accompanies a valvular defect then digitalis may be used with benefit.

In patients with valvular heart disease the myocardium and the coronary arteries frequently participate in the damage. It is not the state of the valves so much as the state of the myocardium which determines whether or not digitalis is indicated.

The practice of prescribing digitalis for patients who show a heart murmur and no evidence of cardiac failure cannot be too strongly condemned. It is a potent source of cardiac neurosis.

In that symptom complex, angina pectoris, the question frequently arises as to the advisability of employing digitalis. There remains much for us to learn regarding this peculiar syndrome. That it indicates grave cardiac damage no one questions. We frequently find at the postmortem marked sclerosis of the coronary arteries and lesions which would suggest that the patient had suffered from angina pectoris and yet after a careful perusal of the history learn that the patient at no time suffered from this symptom. Why it should occur in one individual and not in another with

similar pathological lesions remains unexplained. The pathologist cannot diagnose this condition either from the gross pathological anatomy or with the microscope. Digitalis is as a rule ineffective in combating the attacks and its employment in this condition is generally without avail.

Since Eggleston has placed sanction on larger doses of digitalis untoward symptoms have been more common. If we would keep in mind Eggleston's warning regarding the use of massive doses this effect would be less frequent. In commenting on this dosage Eggleston remarks "the use of large doses is not a safe procedure unless the patient can be under nearly constant observation and unless the effects of treatment can be graphically recorded at frequent intervals." It is not always easy to determine when the maximum or safe dose has been reached. If we obtain the desired result the dosage is adequate and further use of the drug is contraindicated. Frequently however, before we obtain the desired result one or more symptoms of a toxic nature develop to warn us that we have reached the limit of safety as far as dosage is concerned.

Cushny has aptly compared the administration of digitalis by massive dosage to a simple chemical titration in the laboratory. Where the strength of the reagent is known, it is safe to run in from the burette a relatively large quantity of salt, and then complete the reaction with a few drops as the end point is reached.

Bastedo has laid down the following excellent rules as to when to stop digitalis.

1 Digitalization as shown by the electrocardiograph

2 When the desired effect is accomplished, as by the disappearance of dropsy or enlargement of the liver, or by the slowing and steadying of the pulse in auricular fibrillation

3 Nausea and vomiting ensues

4 If the patient complains of headache, anorexia and dizziness or light-headedness

5 The cardiac rate goes below 60

6 The rate slows suddenly

7 Coupled rhythm appears

8 Premature beats occur

9 A regular rhythm becomes irregular or intermittent

10 Sinus arrhythmia or phasic arrhythmia occurs

Carr, from the Cook County Hospital, Chicago, calls attention to digitalis delirium which he has observed and which he feels is frequently overlooked as one of the toxic manifestations of the drug

Quite recently our attention has been called to eye symptoms produced by digitalis. Sprague, White and Kellogg state "these disturbances are very infrequently recognized in this country, in the French and German literature, however, visual disorders from digitalis have been well described." Even Withering himself called attention to this phenomenon and states that occasionally there is noted obscured vision, objects appearing yellow or green. Occasionally symptoms of

toxic amblyopia with dimness of vision, flickering and flashing scotomas, and marked disturbance of color vision occur. It is believed that these visual disorders from the use of digitalis are more common than is generally supposed.

We have attempted to indicate some of the ways in which digitalis may be abused. A remarkable drug, a fascinating remedy to study and when properly employed a drug whose place cannot be filled at present by any other known remedy. A drug, the study of which has employed the time and energy of some of the most brilliant minds in medicine.

Withering, Mackenzie, Cushny, Price, Hatcher, Eggleston, Robinson are some of the names which will probably always be associated with the history of digitalis.

These accumulated data regarding digitalis are a particularly rich heritage which fall to the student of medicine today. It behooves him therefore to employ this heritage properly, to be well versed and familiar with all phases of therapeutic activity of the drug. In his zeal, however, he should ever keep in mind the well defined limits of its field of usefulness. A powerful drug, potent to do harm when used indiscriminately, the margin between safety and danger is a particularly narrow one. Its ability to cause serious damage and even death should never be lost sight of. An agent requiring delicate and skillful handling, its administration should never be left to untrained hands.

# Diabetic Therapy, With Special Reference to the Newer Remedies\*

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THE literature of today is teeming with articles on diabetes mellitus and especially with its therapy, there is probably no subject which has engaged the thoughts of a higher class of medical minds than this one. Such leaders as Allen, Joslin, Wilder and Woodyatt in this country, Banting, MacLeod and Campbell in Canada, and von Noorden, Minkowski, Cammidge and others abroad demonstrate, by their unceasing interest, not only that the riddle of diabetes is fascinating, but that it will be solved! By this, I mean that, whereas, by various methods of therapy, which we shall detail in this paper, the disease may usually be controlled, still we have not yet reached the point where we might put the letters "Q.E.D." after the diabetic problem!

The scope of this paper does not permit of a consideration of the etiological factors in diabetes, except insofar as they pertain to the subject of therapy, I trust that you will bear with me, therefore, while I briefly refer to historical data, leading up to modern treatment. The classical experiments of Claude Bernard, during

which he demonstrated the famous "piqûre" or puncture of the tip of the calamus scriptorius in the fourth ventricle, causing a glycosuria, with depletion of liver-stored glycogen, may be designated as the starting point of thinkers, searching for rational diabetic therapy. As far back as 1682, Conrad Brunner attempted total pancreatectomy on dogs, in trying to solve the etiological problem, it was not until 1889—or 207 years later—that Von Mering and Minkowski successfully carried out this experiment and gave to the world the information that severe and fatal diabetes is caused thereby. Although Paul Langerhans first described the islands in the pancreas, bearing his name, in 1869, it was not until 1901 that Opie demonstrated that these are the elements involved in pancreatic diabetes.

While investigations by the above-named and numerous others were being conducted, both in etiological studies and attempts at specific therapy, what was being done by the army of practical clinicians in treating the increasing number of cases that were presenting themselves? Up to this century, very little progress was made in therapy, it was realized, of course, that carbohydrate metabolism is dis-

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turbed and the sole aim seemed to be to minimize the intake of that food element—too often with quick disastrous results. About 1900, under the influence of the German schools, especially Naunyn and his coworkers at Strasburg, followed by von Noorden and his associates at Frankfort, the dietetic treatment was handled more scientifically, with the results that undernutrition and acidosis were prevented—at least, for longer time—and the average life of the diabetic prolonged, we understand better today than was understood then why von Noorden often got good results with his oatmeal “cures.” Then, about 1914, Allen advanced the method of prolonged fasting and undernutrition, which was first received with misgivings by many who had seen fatal starvation-acidosis, but, it was not long before the skeptics had to admit that, if properly carried out, as outlined by Dr. Allen, it accomplished more for the severe cases than anything yet proposed, Joslin’s statistics on this are thoroughly convincing. An Italian, named Guelpa, also carried out fasting, along slightly different lines, with improved results in his cases.

Diabetic therapy was revolutionized when, on February 22, 1922, Banting and Best, with their associates, first gave out reports of the successful use of their product in human beings, seven cases being reported. Their work followed the researches of Minkowski and the others, above referred to, they had found what workers had been anxiously looking for ever since the announcements of Von Mering,

Minkowski and Opie. In some quarters, the announcement was received with skepticism, while the overenthusiastic expected too much, it was some time before the discovery could be properly evaluated and then it was realized that, with “insulin here” (to use Joslin’s expression), the proper regulation of the diet became of more importance than ever—this, I might add, being to the thorough disgust of many diabetics, who soon formed the idea that, when taking insulin, they could be turned loose in the confectionery. Although some of the best clinicians of today do not agree with him in toto, Woodyatt’s ketogenic-antiketogenic formula of  $F = 2 \times C + P/2$ , with total calories depending upon weight, physical activities, etc., holds good. Opinions differ as to relative amounts of protein and fats, most authorities figuring the protein at 1 gram or less per kilo of body weight, Newburgh and Marsh, for example, believing in a higher fat and lower protein than Allen and his followers, certain it is that most diabetics take proteins better than fats, but the glucose-equivalent of the former is so much more than of fats, that this must be reckoned with, on the other hand, under-nourished diabetics may be built up rapidly with higher fats, in order to increase the total calories, provided the carbohydrate and insulin be also kept comparatively high, in order to obviate the danger of ketosis. In this respect, it would not be amiss to mention the fat-substitute, with the odd molecule, which, it has been shown, is incapable of being converted into acetone bodies, this preparation was worked out by the late Dr. Max

Kahn of New York and named "Intarvin" and, although I have had no personal experience with it, I can readily see where it would prove of great value in arranging the diet of those severe diabetics who are prone to develop this dreaded complication.

As to the administration of insulin, I feel that it is pretty well agreed today that the majority of cases can be controlled by giving it twice daily, before breakfast and before the evening meal, the dose varying according to the diet (total carbohydrate-equivalent and, especially, total calories), severe cases require, sometimes, more frequent dosage and, of course, surgical complications and acute intercurrent diseases necessitate increases, but, what I mean to bring out is that, considering the indications, comfort and mental attitude of any case, two doses per day is generally the happiest solution. It is, usually, preferable to give a larger dose in the morning than in the afternoon, for obvious reasons, from time to time, the dosage has to be varied, as we are constantly, when trying to keep the patient's blood sugar around normal—especially in children—between the Scylla of hyperglycemia with its complications and the Charybdis of hypoglycemic reactions. Although the literature contains reports of insulin-resisting patients, I have been fortunate enough not to encounter any of this genus and am always suspicious, when reading these accounts, that there may be other factors, escaping the watchful eye of physician or nurse, as illustrated by the following case, which came under my observation three years ago. A boy of 12, patient in a charity hospital,

maintained glycosuria and hyperglycemia, in spite of careful dieting and gradually increasing insulin dosage. One day the picture suddenly changed and he was found in profound coma, cold and clammy, his urine was sugar-free and blood sugar was 0.45 after his revival with intravenous glucose, it was learned that his friend had been smuggling fruit and candy to him until that day, when, through the influence of the boy's relatives the supply had been suddenly cut off without apprising the resident physician of the facts.

Other factors, too numerous to mention here might enter into these cases. However, be that as it may, although we have an invaluable therapeutic aid in this preparation, we cannot call it a "cure" in the true sense of the word, we may tide our patients over complications, we may improve the tolerance of the milder cases and we may help all diabetics with it, for, as Joslin says, there must be in addition to the sugar-consuming properties, an indefinite something in insulin, which contributes to the well-being of the diabetic, for this reason, he feels that a small dose, once daily, is helpful even to the milder cases.

In looking for a "cure" and in trying to obviate the hypodermics, so repugnant to some, we hope to find a suitable oral remedy. Dating back to pre-insulin days, various pharmaceutical and biological firms have laid claims to remedies that either palliate or cure the diabetics, some of these claims, I might state, to use an expression which I heard from Dr. Cushing, are "simply harrowing".

It is useless to enumerate the yeast products and the pancreatic derivatives which have been, and still are, offered to us as a panacea for this perplexing disease. However, the most hopeful substitutes for insulin have come from Germany and the Nobel prize commission, which, a few years ago, awarded the honor in medicine to the discoverers of insulin, has seen fit to bestow the same, in 1927, upon Prof. Frank of Breslau for producing one of these preparations, known as "Synthalin." Others which I have investigated and packages of which I am showing you today, besides Synthalin, are Fermocyl, Reglykol, Glukhorment. In a personal communication, Prof. von Noorden states that the first two are not highly considered in Germany and that they are handled over the counter by the pharmacists, whereas Synthalin and Glukhorment are prescribed. Fermocyl is said to be a yeast product, whereas the published formula of Reglykol states that it contains no guanidin or derivative.

My personal experience with these preparations is limited to three cases, in which I have used synthalin, brief details of which follow —

*Case I* A. H., aged 6, diabetes of over 4 years duration, during most of which time he has been on insulin therapy. Tablet of 0.10 gms synthalin given for two nights in succession and then omitted every third night. Patient would get some manifestations of hypoglycemia about 14 hours after administration of drug, this stopped after reduction of morning dose of insulin. No gastrointestinal disturbances.

*Case II* C. S., aged 37, diabetes of 9 years duration, has used insulin somewhat irregularly, for past 4 years. Tablet of 0.25 gms synthalin taken twice daily for two days and omitted on third. Was able to reduce insulin materially, but finally quit

the synthalin, as he said that the reducing of blood sugar made him weak and he did not know how to control it, as he did with insulin dosage. No gastrointestinal symptoms.

*Case III* S. C., aged 6, diabetes of 6 months duration, during most of which time she has been on insulin. Took 0.10 gms synthalin every night for three nights, then skipping one night, results same as in first case and no gastrointestinal symptoms.

Synthalin is a synthetic compound, *de*-camethylene-diguanidine, introduced by Frank and associates, from Minkowski's clinic in Breslau in December, 1926, practically all the reports give it credit for reducing blood sugar, but it is generally claimed that the gastrointestinal irritation produced by therapeutic doses prohibits its general use, the firm of Kahlbaum, which placed it on the market, claim that it acts like insulin, by supplying something to the system, which produces glycolysis. An interesting discussion has arisen in Germany on this point, one observer contending that its effects are liable to be harmful, in that its results are obtained only by overstimulating the already weak internal-secreting islands of Langerhans, this contention, however, is vigorously denied by the sponsors of the drug. I wish to call attention to the fact that, in my limited experience, no irritation of digestive tract was observed, but I have discontinued use of the preparation, partly on account of the warnings and partly because of difficulty in obtaining it in this country. A few months ago, Eli Lilly & Co., who, it will be remembered, were the first in this country to produce a commercial insulin, under license from the Toronto group, undertook an investigation of synthalin, with the idea

that, if reports justified, they would handle it, commercially, in the U S. Under date of February 6, they inform me that they are still investigating this product, as well as a later one, neo-synthalin, but that they are not yet sufficiently satisfied to justify making definite statements, further, that Prof Frank recently visited their laboratories and agreed with them in their conservative attitude, they state, also, that neo-synthalin appears to be less liable to produce gastrointestinal irritation than its precursor. Dr A I Ringer of New York who has been investigating these preparations, writes me, under date of February 20, that, although he has seen decided lowering of blood sugar, with disappearance of glycosuria, still he hesitates to recommend synthalin, owing to its frequent gastric irritation, as to neo-synthalin, it has been inert in his hands.

Now, concerning Glukhorment. When a relative of mine was in Karlsruhe, last year, he made inquiries for me concerning synthalin, he was told that it was feared, on account of the digestive disturbances, but that a newer and better preparation, in use there, was Glukhorment, it being endorsed by Prof von Noorden. I have never tried it, personally, but, some time later, I read that von Noorden had withdrawn his endorsement therefrom, anxious to know the truth, at least before using it on a patient, I wrote to him and he was kind enough to reply freely, part of which I quote below —

“Glukhorment is an undoubtedly effective and useful preparation and decidedly more agreeable than Synthalin, even though it may be better

sometimes to pause one or two days, after a 3 to 4 days' use, on account of the stomach.

According to the present state of investigation, there is no doubt but that there is present in Glukhorment, in a considerable quantity, a chemical body which is similar to and possibly even identical with Synthalin. As I already said in my paper of November 8, 1927, the chemist of the Horment Company still absolutely denies that Synthalin is added while, on the other hand, the Schering factory in Berlin, manufacturers of Synthalin, declare the opposite. As it is impossible to decide the question, definitely, by chemical analysis, the two interested powers have, with my consent and, partly on my suggestion, sued each other in the courts. From the resulting evidence and testimonies, the actual truth will be finally determined.

In my clinic, we have ceased long ago, even before the advent of Glukhorment, to administer Synthalin, as the concomitant disturbances were too frequent and intensive.”

Prof von Noorden also referred me to an article by Prof Dale of London, published in the British Medical Journal of December 3, 1927, in which he shows proof that, in spite of von Noorden's statement to the contrary, either synthalin or a similar guanidine derivative is present in Glukhorment, when Prof Dale apprised von Noorden of his findings, he (von Noorden) had just received similar disconcerting evidence from another quarter, this, then, is what gave the impression that he had renounced Glukhorment—he did not renounce it in toto, but he asked the medical world to suspend judgement, on the strength of his

statement that it contains no synthalin or other guanidine derivative until the truth may be brought to light, as outlined in his letter

All of the above strikes us as a tribute to the effectiveness of synthalin! Now, Dr Ringer, who, as above stated, has noted the decided lowering of blood sugar with synthalin, informs me that he has noted no such effect, whatsoever, from glukhorment

A paper of this kind would be incomplete were it not to call attention to the various products of the vegetable kingdom that have been used with more or less success and, especially, refer to the interesting and hopeful work of Allen with myrtillin

Natives in various rural districts have empiric knowledge of the action of decoctions or other preparations of domestic plants in lessening polyuria, which is so often (might we say, usually?) glycosuria. In Prof von Noorden's lectures on diabetes, delivered in this country, in 1905, he stated "About 15 years ago, Prof Binz and Dr Graser discovered that the fruit of the East Indian plant, *Syzygium jambulanum*, possesses the property of strongly reducing phloridzin diabetes. As both the dried fruits and their extracts have proved themselves to be quite harmless even in large quantities, it is not surprising that new experiments are always being made to see whether the glycosuria of true diabetes cannot be alleviated or cured by it. I have,, myself, employed and studied the effect of jambul preparations on cases of severe and slight diabetes, the results showed that, in some cases, a marked effect on the glycosuria was, without doubt, actually obtained"

Not long ago, Root and his associates in Joslin's clinic called attention, in an article in the Archives of Internal Medicine, to the beneficial effect of "Jerusalem artichokes" in many cases, they mentioned the fact that the starch in this form not only does not raise the blood sugar, but that, often, while getting nourishment, the diabetic has been known to acquire an increased tolerance while using this root-article of the potato family, properly prepared

Allen tells us that, in certain districts in Hungary, the peasants have known for years that a decoction or tea of certain blueberry leaves helps the polyuric, on this information, conveyed to him by his chemist, he has experimented with the preparation which he has named "Myrtillin". While he makes no extravagant claims for it, he states that, given an adult diabetic whose blood sugar has been brought to normal, with diet and insulin, myrtillin will, as a rule, keep him in good condition, which is certainly encouraging, to say the least

To sum up, then, we feel that the outlook is bright for more help for the large army of diabetics, we believe that, although, for the present, our main reliance shall continue to be insulin and proper diet, the many investigators working on this problem will soon be rewarded, especially, do we feel that Frank and his associates have blazed a trail and that something on the order of synthalin will soon be found, which will prove a boon to these unfortunates and will replace insulin, as a routine, but not of course in coma, surgical complications and in very severe acute cases

# A Consideration of Natural and Acquired Body Resistance to Neoplasia\*

By J L GOFORTH, M D, *Dallas, Texas*

**D**ESPITE extensive investigation and experimentation in practically every possible line of study in the field of neoplasia, so little has been learned that the cancer situation still confronts the medical profession as a baffling and largely unsolved problem. It has not been demonstrated that the body tissues can develop immunity to neoplasia, either naturally or artificially, and until the causes and more of the nature of the disease are determined, immunology probably will be of little aid in combating it. The body tissues, however, do build a type of resistance of greater or lesser degree, to neoplasia in the majority of instances. The activities of this defense mechanism are recognizable and demonstrable microscopically chiefly, and are evaluated in the analysis of the relationship that exists between host and neoplasm—a procedure which is essentially a histopathologic study. The age of the patient, the duration of signs and symptoms, the location, gross form, and extent of the tumor are all important indices to prognosis from the

clinical point of view, but are not considered in this study.

Many diseases are associated with increased or diminished rate of multiplication of some of the specific component cells of the body. Whatever the etiology of cancer may prove to be, whether a parasitic, a physiologico-chemical change in certain groups of cells, a cellular response to continued chronic infection and irritation, a spontaneous growth-impulse occurring in cells which are misplaced anatomically, or an hereditary phenomenon, it seems certain that some stimulus, as yet unknown, possesses the definite capacity to cause local multiplication of cells that have apparently functioned as normal cells prior to the action of the stimulus. This lawless proliferation of cells is neoplasia, and the reactions of the body tissues to this misdirected and anarchic growth-impulse constitute the host's natural defense mechanism.

Strauss (1), in an interesting study based on the thought that the observance of the spontaneous disappearance of clinically and histologically malignant tumors might throw light on the working of the natural protective mechanism of the body tissues to neoplasia, this in turn leading to methods

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of increasing body resistance which would be of therapeutic value, found only 53 cases in the literature which he accepted as spontaneously disappearing malignant neoplasms. This would tend to show that natural resistance unaided is able to overcome neoplasia in small measure only. It is my purpose to try to show that in dealing with neoplastic disease, the proper procedure will have not only a destructive effect on the growth locally, but also will augment and strengthen the working of this natural defense mechanism.

Microscopic study of tumor tissue not only permits of the classification of the neoplasm, but establishes its structural form and cell-type, and gives valuable information regarding the reaction of the body tissues to the invading tumor. Cancer cells tend to reproduce the cell-type and structures from which they are derived, and the rate of growth of a given tumor determines in a large measure the degree of perfection of this tendency. Just as the normal growth impulse of tissues tends to wane as the body ages, in neoplasia, as a general rule, the older the patient is, the slower does the tumor grow, the later does it metastasize, and the more differentiated is its cell-type likely to be.

Cell-type determination is particularly important in that the information thus afforded regarding the degree of maturity of the predominating cells composing the neoplasm is of guiding value in the choice of treatment procedure. Cells of immature or undifferentiated type, exert so much of their energy in reproduction that

they do not have time to approach the mature form which their prototypes normally assume. They grow more rapidly, and by reason of their embryonal nature, are more vulnerable to certain destructive physical agents, such as radium and the roentgen-ray, than those of greater differentiation, or more adult type. The seeming handicap of rapid rate of growth common to those neoplasms composed of unripe cells often may be partly offset because of the "radio-sensitiveness" of the tumor cells. The degree of differentiation of neoplastic cells is so readily estimated that it has become a routine procedure in several cancer clinics. A frozen section preparation of a small sample specimen of tumor tissue is sufficient for the determination in the hands of a trained tissue pathologist. It is my feeling that each case of neoplastic disease should be treated as an individual problem, and the general plan of attack should include biopsy study of the tumor tissue as early as possible in order that cell-type and differentiation determination may serve as a guide in the choice of the therapeutic agent to be employed. Such procedure is both rational and scientific in the present state of our knowledge of cancer.

The activities of the several natural factors of body tissue defense vary considerably in the different types of neoplastic disease. Fibroplastic tissue proliferation occurs spontaneously in greater or less degree about the advancing edge of many neoplasms. This fibrous tissue often gradually condenses, becomes very tough and firm, and may undergo hyalinization. The resulting scirrhous mass may be

thought of as an ever-constricting network of local body defense enclosing and attempting to obstruct, limit and choke the progress of the new growth. It is a well established fact that irradiation promotes fibroblastic tissue proliferation locally. In those instances where the use of radium or roentgen-ray, or any other fibrous tissue stimulator, is indicated, the treatment may be regarded as actually augmenting body resistance in addition to its primary function of destroying the neoplasm.

The spleen has been an interesting subject of study and experimentation because of its well known antagonism to neoplasia. In a series of 6500 necropsies, Krumbhaar (2) found only 40 splenic tumors, 21 of these were secondary carcinomatous growths, and 12 were sarcomatous deposits. It is noteworthy, too, that lymph nodes receiving drainage from tumor-bearing areas frequently exhibit a remarkable proliferation of sinus endothelium. Jaffé (3) states that metastases are less frequently found in nodes showing endothelial hyperplasia than in those where the endothelium has not reacted. Such a tissue reaction occurring in the major reticulo-endothelial centers finds a possible explanation in the anticancerous action of the reticulo-endothelial cells themselves, and when it is recalled that wandering endothelial cells or clasmotocytes of phagocytic capacity are frequently demonstrable about the advancing borders of malignant growths, the function of the reticulo-endothelial system as an important agent in the defense of body tissues against neoplasia seems quite plausible. Jaffé (3) in a recent

interesting study of the rôle of the reticulo-endothelial system in pathologic conditions found that the cells of this system could be influenced therapeutically. A reduction of the endotheliocytes follows splenectomy, and roentgen-ray applications in small dosages, the injection of non-specific proteins, and the intravenous injection of certain dyes and colloids all tend to stimulate these cells to multiplication and activity. As more is learned regarding the actions and behavior of this widespread and wandering body tissue, the possibility of mobilizing and employing it in the attack on cancer through the use of stimulative therapy is strongly suggested.

The local accumulation of large numbers of lymphocytes and plasma cells in addition to the endotheliocytes above referred to, constitutes a defense measure frequently employed by the host in combating chronic progressive infections of many types. In neoplasia the gathering of these cells throughout the tumor and fibroblastic tissues surrounding the growth is often observed, particularly when there is associated with the neoplasm a chronic, secondary infection. In studying the responses and reactions of the tissues of the body protective mechanism to various methods of tumor therapy by means of repeated biopsy examinations at different periods of the tumor's course, I have often noticed a progressive increase of this mononuclear infiltration locally as the neoplasm yields to treatment. It has not been definitely determined whether these cells can be influenced therapeutically, but I believe they play some rather important role in inhibiting the



extension of both the infection and neoplasm

In another study (4), the eosinophil was considered as having protective properties against neoplasia. Relatively little is known about the eosinophil, or its function. It has long been known that the eosinophils increase in number in intestinal parasite infestations, bronchial asthma, anaphylactic and allergic reactions, certain chronic diseases of the skin, and certain chronic inflammatory processes such as pleural effusions, chronic active appendicitis, and chronic pelvic infections. It is also usual to find an eosinophilic infiltration of the tissues which are the seats of these conditions. In myelogenous leukemia, which may be considered a form of neoplasia, striking eosinophilia is the rule. In the study of squamous cancers of all locations, and the adenocarcinomas of the gastrointestinal tract, I have been impressed with the observation that in those instances where local eosinophilia has obtained, the patient has exhibited a greater resistance to the neoplasm, has responded better to treatment, and has lived longer than when eosinophils were not present. In a recent study of 417 radiologically treated cases of squamous carcinoma of the cervix, Schoch (5) found that in the 40 cases with local eosinophilia the proportion of five years cures was 45%, while in the three hundred and sixty-seven cases without eosinophilia, it was only 10%. In a recent analysis of the behavior of the several body defense tissues in a group of epidermoid cancers of the cervix which I have followed, especial attention was given the eosinophil. This study indicates (1)

that the eosinophils in the circulating blood, as determined by the differential count, increase in percentage as the eosinophilic infiltration of the tissues about the neoplasm becomes more prominent, (2) that the greater the number of eosinophils both locally and in the blood stream, the more favorable is the prognosis, and (3) that irradiation tends to promote eosinophilic activity and multiplication. I regard the presence of the eosinophil as a good omen in malignant disease, and consider it a valuable index to prognosis in addition to its being an important defense agent against neoplasia.

In the light of these considerations, the logical and rational treatment of cancer resolves itself into a plan of attack having a double objective, namely, (1) the eradication of the disease locally, and (2) the augmentation of the patient's natural resistance to further or recurrent neoplastic growth. This, I feel, may be best accomplished by routine thorough study of each neoplasm both grossly and microscopically, followed by the application of the form of treatment best suited to the individual neoplasm. It has been demonstrated that certain tumors will respond well to one method of treatment, and poorly to another. The information obtained through the procedures and considerations above outlined enable one to forecast relatively accurately the response that may be expected of a given neoplasm to the various methods of therapy, and, in my experience, has proved a very helpful guide both in the selection of the therapeutic agent of greatest prob-

able efficiency, and in the method of its application

Without attempting to evaluate in detail the relative merits of the several standard methods of neoplasiotherapy at present in use, I wish to point out that radical surgical procedure has apparently very nearly reached its high point of efficiency in combating neoplastic disease in several locations that are favorite sites for tumor growth. There is a tendency to determine the operability of a neoplasm from the gross or clinical point of view. When it is recalled that infiltrative neoplasms often extend far beyond the area that forms the gross tumor mass, it is evident that many so-called operable growths are in reality quite inoperable. Attempted surgical extirpation of such tumors fails not only in the eradication of the disease but actually interferes with and curtails the activities of the natural body defense mechanism to neoplasia. A certain group of neoplasms belong properly to the field of surgery, and I feel that surgical activity should be limited to these.

Radium and roentgen-ray therapy, properly and scientifically employed, have proved very efficacious in both arresting and eradicating certain types of neoplastic diseases. As pioneer agents, relatively speaking, they promise much in the further development and extension of their usefulness in the attack on neoplasia because of their destructive action on the large group of radio-sensitive tumors, and their stimulative effect on several of the body defense tissues.

The combined employment of surgical methods and radio-therapy, with, in appropriate cases, the additional aid of adjuncts such as the cautery and

electro- and chemo-therapy, offers an approach to a third large group of neoplasms that yield neither to operative procedure nor irradiation alone. The use of the cautery in destroying much of the tumor largely for facilitating the more accurate and efficient placing of radium has given excellent results in many instances. In many of the so-called "hopeless cases" of cancer, combination therapy, as above indicated, while not curative, often retards the progress of the disease, thus affording additional time for the working of the body defense agents, and offers the patient temporary relief from the ravages of the disease.

As the proper information regarding cancer is disseminated among the laity, the various types of malignant disease will be seen in earlier stages, and differential diagnosis correspondingly will become more difficult. In order that each patient with a tumor complaint may be given the obvious advantage of the indicated treatment at the earliest possible moment, it is apparent that all anticancerous forces must be called into united action. The cancer problem does not belong exclusively to any one of the major divisions of medicine, it is a problem facing the entire medical profession, and only by combining the tumor knowledge, the various aids in diagnosis, and the different methods of treatment of the fields of surgery, internal medicine, radiology, and pathology can any headway in the conquering of neoplasia be hoped for.

#### SUMMARY

1. An analysis of the relationship that exists between host and neoplasm

is presented The reactions of certain body tissues to neoplastic growth constitute the host's natural resistance to neoplasia

2 The histologic type of tumor cells, particularly the degree of differentiation of the predominating cells of a neoplasm, is a reliable criterion upon which to base prognosis from the pathologic point of view, and should serve as a guide in the choice of the therapeutic agent to be employed Biopsy study should be an early routine procedure in the plan of attack on each malignant neoplasm whenever possible

3 The activities and behavior of the several tissues playing rôles in the body protective mechanism against neoplasia, are evaluated as follows —

(a) The proliferation of fibroblastic tissue about the advancing edge of many neoplasms tends to limit and obstruct the progress of the growth Radiotherapy stimulates the activity of this defense factor

(b) The antagonism of the reticulo-endothelial system to neo-

plasia is discussed The possibility of influencing endotheliocytes therapeutically in the attack on neoplasia is suggested

(c) Lymphocyte and plasma cell infiltration of and about tumor tissue tends to inhibit the extension of the neoplasm and the secondary infection that is often present

(d) The eosinophil is a valuable index to prognosis in addition to its being an important defense agent against neoplasia

4 The rational treatment of neoplastic disease should have a double objective (1) the eradication of the tumor locally, and (2) the augmentation of the host's natural resistance to further or recurrent neoplastic growth Each case of malignant disease should be considered as an individual problem, and the form of treatment best suited to the growth as determined by the several reliable guide factors above mentioned, should be applied

5 The cancer problem faces the entire medical profession and calls for united and cooperative endeavor from each of its special divisions

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# The Influence of the Tropics on Rickets\*

By COL ROGER BROOKE, *U S Army, Fort Sam Houston, Texas*

**A**BOUT the year 1650 Glisson, the distinguished English physician and physicist, as the result of an extended study concerning what was believed to be a new disease, published a monograph on rickets. Since the appearance of his notable paper down to scarcely more than a decade ago, progress in our knowledge of this common disease of childhood has been slow and of little clinical value. During the past ten years, however, many material and valuable discoveries have been made, due in great part to the able investigations of Mellanby, Huldschinsky, Howland, Schmorl, Findlay, McCollum, and that tireless and fruitful worker, Hess, of New York. In spite of the many advances made in our knowledge of rickets in recent years, much remains to be learned, especially as to details of etiology.

What I shall have to say today is based upon a review of the recent literature, a study of 100 white and 100 negro children in Panama in 1925 and 1926, and a few observations made in New Mexico and the Philippine Islands fifteen or more years ago.

It is believed that a brief summary of the more important discoveries in

respect to and current views on rickets will facilitate the orderly and logical consideration of my theme.

It is generally recognized that rickets is a constitutional disease of infancy manifested by disorders of nutrition and metabolism. The most obvious disturbance is an inability of the organism to deposit or fix calcium phosphate in the growing bones. As a result, the bones lose calcium, become soft and in advanced cases bow or bend. Long bones grow at the epiphyseal junction. In rickets, marked and characteristic changes occur at this line, to wit: marked proliferation of the osteoid cells, failure to take up or retain calcium, increase and ingrowth of capillaries from the diaphysis to the epiphysis and thickening of the periosteum due to a deposit of cartilaginous and osteoid tissues about the cortex. These pathological changes give rise to enlargement and softening of the epiphyses, especially those at the wrists, ankles and costochondral junctions. Normally the epiphyseal line as depicted in the X-ray film is straight and well defined, in rickets, due to the afore mentioned changes, it becomes ragged and ill defined. The flat bones of the head and pelvis may lose so much calcium as to crackle and crumple with result-

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ing deformity of the cranium and pelvis

Many other equally important, however less obvious, changes take place. The muscles become soft and flabby, the nervous system irritable, and the lymph tissues proliferate. The blood calcium normally 10 to 11 mg to 100 c.c. of volume may be normal or reduced in amount. The inorganic phosphorus content—normally 5 mg per 100 c.c. of serum—is quite constantly and materially reduced. From the diagnostic standpoint the phosphorus level has assumed importance. In rickets manifested by tetany the calcium is low and alkalosis often present. When the calcium is normal the tendency is toward acidosis. Howland states that rickets does not occur unless the product of the calcium and phosphorus content in mg per 100 c.c. of serum falls below 40 to 30.

Why the bones are unable to fix calcium, in spite of the fact that the blood level may be normal, is one of the many unsolved problems in rickets. Some believe the absorption of calcium from the intestines is just sufficient to maintain the normal blood level, but is inadequate to permit utilization by the bones. Others that absorption is normal but excretion excessive. And finally, still others that neither absorption nor excretion are faulty but that the bone cells are unable to fix and retain calcium due to an insufficient supply of the antirachitic factor often termed vitamin D.

McCollum and his co-workers found that in animals the ratio between calcium and phosphorus in the diet is very important and may be of greater significance than the absolute amounts

present. Present day evidence is to the effect that an infant's diet is rarely or ever so deficient in minerals as to be an important factor in the production of rickets.

Mellanby discovered in 1918 that many animal fats contained a substance which would prevent rickets. He originally regarded this as vitamin A (fat soluble). McCollum ascertained in 1922 that the active body was not vitamin A and designated it the antirachitic factor. In the literature of today it is frequently termed vitamin D, however, many investigators object to this appellation on the ground that its identity is as yet undetermined. It is the principle so abundant in cod liver oil and so potent in the prevention and cure of rickets.

In 1919 Huldshinsky made the epoch-making observation that ultra-violet rays generated by the mercury quartz lamp would cure rickets. Two years later, A. F. Hess discovered that the ultra violet rays of the solar spectrum were likewise efficient in the prevention and treatment of rickets.

It is now generally conceded that three factors play a rôle in the etiology of rickets:

- 1 Ultra-violet rays
- 2 The antirachitic factor commonly called vitamin D
- 3 Unbalanced diets

Most authorities regard an insufficiency in quantity or quality of ultra-violet rays as by far the most important factor in the production of rickets in children. A deficiency or disproportion in the ratio of calcium and phosphorus is rarely a cause of rickets except in experiments on animals.

It is generally accepted that rickets is uncommon in the tropics and mountainous regions where sunshine is plentiful and an abundance of solar ultraviolet rays present. Why ultraviolet rays are so abundant under the conditions mentioned will be explained later on.

It has been common knowledge for years that rickets is also rare in the Arctic Zone and certain other localities where the amount of sunshine is small and the humidity high, as in the Baltic Basin, the Hebrides, and Western Ireland. In such regions it is obvious that sunshine plays a small part in the prevention of rickets. The inhabitants in these regions subsist largely on fish, animal fats and livers, even the small children begin to eat blubber and liver before they can walk. All these foods are exceedingly rich in vitamin D. We are therefore justified in concluding that the antirachitic substance, provided it is freely taken, will prevent rickets in children even though living in insanitary environments and with a scant supply of ultraviolet rays. We have other evidence of the potency of vitamin D in the prevention of rickets. Hess, and others, have shown that many foods containing cholesterol and sterols can be so activated by irradiation with ultraviolet rays as to prevent rickets in an animal on a diet that is ordinarily rachitic producing. Powdered milk, dried brain tissue and yeast are particularly favorable foods to activate and if properly stored will retain their potency for six months. Many vegetables contain phytosterol, the counterpart of cholesterol in animal foods, which also can be activated

by the ultraviolet ray and therefore utilized in the prevention of rickets. Carrots and spinach retain their activity after they are cooked, but are not nearly as potent as milk, eggs, brains, liver, yeast and animal fats. Fruits, cereals and starches contain so little sterol that irradiation does not render them effective antirachitic agents, according to Hess.

Three percent cholesterol in olive oil after activation by the mercury quartz lamp is very efficient in curing rickets. Activated cholesterol may be used to fortify cod liver oil, but strange to relate, irradiation of the latter does not increase its potency, on the contrary, it appears to lessen it. Hess has found that irradiation of pure cholesterol is ineffective, apparently it must contain an impurity in order to be activated. Recently this diligent investigator has reported a sterol—known as ergosterol—as the most potent antirachitic substance known. It is so powerful that he thinks it may be the antirachitic vitamin. Activated ergosterol is 500 times as potent as irradiated cholesterol. Five mg is about the equivalent of one liter of cod liver oil and 0001 mg daily will prevent rickets in a rat on a rachitic diet. It is believed to be the constituent of cholesterol, sterols and foods that are activated by irradiation with ultraviolet rays. As far as I can ascertain it has not been used in the clinic in the pure state. Irradiated yeast from which ergosterol may be extracted is one of the forms in which it has been administered.

Gerstenberger states the ingestion of cod liver oil by the mother will not

prevent or cure rickets in her breast-fed child, that is, the antirachitic factor in cod liver oil is not transferred to the infant through the milk. On the other hand, if the mother herself is irradiated with ultraviolet rays her breast-fed infant will not develop rickets, or if sick will be cured. It would be logical to infer, therefore, that the vitamin activated by the ultraviolet ray is secreted in the milk or is much more powerful than that found in cod liver oil.

Before considering how the tropics influence rickets, a few remarks as to climatology, solar radiation and ultraviolet rays are essential.

Most tropical climates have a wet and dry season. The humidity is invariably high during the wet period, and in places is relatively high during many of the dry months. In the tropical zone the length of the day does not vary much between winter and summer. In Panama and Manila for example, the sun sets between 6 15 and 6 45 P. M. throughout the year. When the sun is vertical or even approximately overhead as it is at midday during the summer months in temperate climates, the solar rays transverse a minimum of the earth's atmosphere and comparatively few are absorbed, therefore, the heat, light and ultraviolet rays are commonly said to be hot, bright and intense.

Early in the morning or late in the afternoon the rays reach the surface of the earth at a tangent or nearly so, and consequently, many of them are filtered out by the atmosphere and are weak or few in number.

In the tropics at midday the sun is always approximately overhead,

therefore the rays are always intense at this time, provided the sky is clear. In temperate zones at the noon hour during the winter months the sun's rays are oblique and hence never powerful.

In mountainous districts even in temperate climates the atmosphere is less dense than at sea level and fewer rays are filtered out.

Other factors influence the intensity of the sun's rays, namely humidity, smoke and dust.

The number of sun spots are said to influence the quantity of solar ultraviolet rays given off but as they are not subject to our control and as I have not the qualifications, I will not discuss this feature further.

Heat rays (760 millimicrons in length) constitute 60% of solar radiation, visible or light rays (760 to 380 millimicrons) 40% and ultraviolet rays (313 to 290) less than 1%. The shorter the ultraviolet ray the more effective it is as an antirachitic agent. Ultraviolet rays generated by the mercury quartz lamp are much shorter than the solar rays and therefore more potent, some authorities estimate 30 times as powerful.

Dorno estimated that at Davos, Switzerland, the content of midday sun in ultraviolet rays for the month of January is only 10% of that for July. At the same time the short potent rays (296 to 290 millimicrons) failed to reach the earth's surface during midwinter.

At the latitude of Toronto, Canada, Tisdell and Brown ascertained that the sun's rays for the winter months have only a slight antirachitic effect, but a sharp increase took place in March, and

in May they were eight times as strong as in January. In their opinion this great difference is due more to the absorption of the short potent rays in the winter months than to a material reduction in number.

The term *skyshine* is used to designate the sun's rays reflected from the sky and clouds in contradistinction to the rays received directly from the sun. Thus an object on the sunny side of the street receives both direct and reflected rays, while one on the shady side receives only reflected rays (*skyshine*). An object in the open but covered by a long cylinder with an open end pointed directly at the sun receives only direct rays (*sunshine*). The antirachitic effect of *skyshine*, according to Tisdell and Brown is only from one-half to two-thirds as great as *sunshine*. According to the same investigators sun's rays passed through ordinary window glass have practically no antirachitic effect. Even the special window glass on the market absorbs from 50 to 75% of all ultraviolet rays. In order to obtain material antirachitic effect within a house in temperate climate, the windows must be open and the child placed in the direct rays of the sun.

During a four year residence in New Mexico at an altitude of over 6000 feet the writer saw very few cases of rickets, all of which were of a mild type. In Southwestern New Mexico, the humidity is low, the atmosphere free of smoke, the sunlight intense, and the number of rainy or cloudy days less than at any military station in the United States. The average annual precipitation during my stay was approximately 11 inches.

The weather was so mild even during the winter months that most of the people spent the greater part of the day on their porches or in the open. All these factors would tend to give a maximum of solar ultraviolet rays for the latitude concerned.

The morbidity rate of rickets in the tropics is still a moot question. Everyone concedes that it is less frequent than in temperate climates. A colonial health officer of Trinidad reports that he has not met with a single case in twenty four years. Another one from Jamaica states that it practically does not exist on that island. A doctor from Panama writes, "I have yet to see my first case of rickets in the West Indian negro child." Many doctors have expressed the opinion that rickets is less common among the negroes in the tropics than the whites.

With a view of determining the incidence of rickets in the Canal Zone, Panama, I participated in a survey of children between four months and three years of age. Practically all of the white children—100—of that age were surveyed. This series was given a clinical and X-ray examination. The determination of the blood phosphorus level was not made.

A survey of the negro children, on account of the number and other difficulties, was deemed impracticable. Therefore, 100 of this group on admission to the medical service of the hospital were given a careful clinical examination as to the presence of rickets. The children were stripped and special attention paid to the head, thorax, wrist, ankles and costochondral junctions for evidence of enlargement, change of contour, *craniotabes*, and



beading Unless a rosary was obvious to inspection, beading was regarded as absent The fontanelles, teeth, spine and abdomen were all carefully noted In the white series the mothers were questioned as to restlessness, head sweating, loss of appetite and pallor

A clinical diagnosis was not recorded unless the child presented a typical rosary, characteristic enlargement of the wrist or ankles or unmistakable curving of the legs or two or more of the following signs Cranio-tabes, postural kyphosis with pot belly, tetany or distinctive deformity of the chest

Of the 100 cases in the white series, five presented typical rosaries or such characteristic enlargement of the epiphyses, that they could be recognized at a glance Five others presented questionable enlargement of the epiphyses but associated with such pronounced secondary signs as to justify, in my opinion, the establishment of a diagnosis Six others presented equivocal evidence as to changes in the epiphyses, chest and spine but had delayed dentition, large fontanelles, marked restlessness, head sweating, pallor or loss of muscle turgor This group was treated for rickets but not diagnosticated as such

The X-ray films of 98 of the white series were examined by Dr A F Hess who reported as follows

- 11 Cases very definite rickets
- 7 Cases doubtful
- 15 Cases of healed rickets

"If we were to add the cases of active rickets, of suspected rickets, and of healed rickets, we would have thirty-three cases in all which would

indicate one-third of the infants had rickets

This may be somewhat too high a percentage but judging from a considerable experience in this field, I feel that we can be tolerably certain that one-fourth of these children have rickets

My conclusion is that you have considerable rickets of a mild type in Ancon in spite of the fact that most of the infants are breast fed "

The negro series comprised children admitted to the hospital almost wholly for diseases other than rickets, most of whom were breastfed until one year old Twelve cases presented definite clinical evidence of rickets, eight cases presented equivocal clinical evidence of rickets Two of the negro series had typical tetany and three others obvious bowing of the legs None of the white series exhibited curving of the legs or tetany I feel confident that if the negro group had been X-rayed that a larger number would have shown evidence of rickets The figures show that I overlooked a number of cases, especially healed rickets, in the white series, and it is reasonable to assume that I failed to diagnosticate an equal number in the negro group

In 1903 I examined fifty-two native children in a small town in the Philippines and found that eight had typical evidence of rickets (15%) and five others equivocal signs (10%) In the early days a moderate amount of bowing of the legs was not uncommon in the island of Luzon Practically all of the infants at that time were breast-fed

In my opinion these figures support the view that rickets of a mild type is much more frequent in the tropics than the literature of the past fifteen years would indicate. Advanced rickets and rachitic deformities are certainly uncommon.

In Panama and the Philippines the food of the average family consists largely of cereals, fruits and vegetables—a diet now known to be poor in the antirachitic factor. A large percentage of the infants are breast fed, not infrequently until the child is fifteen or eighteen months old. In spite of the custom of protracted lactation, supplemental feeding of rice, bread, banana, etc. is started early.

To the best of my knowledge the habits of the Esquimaux, Laplanders and other races in the Arctic Zone are similar as to nursing and early supplemental feeding. There can be no question but that the diet of the native in the tropics is much poorer in the antirachitic properties than that of his brother above the Arctic Circle. On the other hand, the resident of the tropics has a bath of ultraviolet rays nearly every day. Quite obviously the inhabitant of the far north and regions overcast by clouds and fogs, much of the time, has the benefit of few ultraviolet rays to activate the sterols in his system.

From the above it would appear logical to conclude that a resident of the tropics secures his relative immunity to rickets from the quantity and potency of the ultraviolet rays in his environment. On the other hand, it is just as reasonable to infer that the Esquimaux obtains his relative immunity as a result of a diet rich in

vitamins. The ultraviolet rays influence the incidence of rickets in the tropics both directly and indirectly.

**Directly** While most infants are not exposed to the direct rays of the sun frequently until they are able to walk, the majority of them receive a liberal amount of skylight, (reflected rays) due to the fact that houses in the tropics have ample veranda space, or lacking this, large doors and wide windows that are usually open. As soon as the child is able to walk most of them find the sunshine, provided the mother is not unduly solicitous about the child's complexion.

**Indirectly** During the period that the infant is breast fed the mother usually comes in direct contact with the sun's rays several hours a day. Gerstenberger has shown that adequate exposure of the mother to the ultraviolet rays results in the prevention of rickets in her breast fed infant. While I do not know of experimental proof, it is certainly logical to assume that milk from cows and goats in the tropics is likewise rich in the antirachitic substance. All food that grows above the ground and that contains sterols should be activated by the sun's rays. It is true, however, that many of the tropical foods are poor in cholesterol and that only a few as spinach, cabbage, etc., are thin enough to be penetrated by the ultraviolet rays, therefore, the practical benefit from the activation of food by the sun is probably slight. At first blush it would appear that rickets should never occur in the tropics. How, then, do we account for the fact that about 25% of the children develop it, albeit in mild form? Most tropical countries and all

that I am familiar with, have two seasons—wet and dry. The wet season usually comprises from seven to nine months of the year. During this period the humidity is high and there are many cloudy and partially cloudy days. Obviously when the sky is overcast with clouds few if any ultraviolet rays reach the earth's surface. Humidity during the wet season often approaches the saturation point. Physicians tell us that high grades of humidity obstruct many ultraviolet rays. Some women, particularly the newcomers to the tropics, rarely venture out of the house during the heat of the day and likewise would consider it unjustifiable, if not criminal, to permit their infants to bask even in the reflected rays of the sun. I venture the prediction that as soon as the important factors relative to the etiology of rickets become common knowledge that this prevalent disorder of nutrition will disappear from the

tropics, except in those parts that have a protracted wet season, excessive number of cloudy days—or what is equally deplorable old foggy parents who are not amenable to reason.

#### SUMMARY

1 About 25% of children in the tropics have rickets. The disease is usually of a mild type. Severe rickets and marked rachitic deformity are rarely observed.

2 Long wet seasons—and high humidity favor the development of rickets.

3 Diet poor in sterols is a less important factor.

4 Proper knowledge by the layman in the tropics of the etiology of rickets should result in the practical disappearance of the disease in all but the cloudiest areas.

# A Study of the Variable Factors in the Use of the Wright's Stain\*

By ROY F. FEEHSTER M.D., D.P.H., *New Orleans*  
(From the Department of Bacteriology and Pathology of Tulane University)

**D**URING the last three years, while engaged in collecting and staining blood smears in quantity to be used in demonstrating to students the various pathological conditions of the blood, we have experienced considerable difficulty in obtaining constant results with the Wright's Stain as employed in the usual way. In trying to eliminate these variations we have studied the results obtained from various aspects and the following outline will illustrate most of the factors responsible for our failure to obtain uniform stains

## DIFFICULTIES WHICH MUST BE CONTROLLED

In a large number of cases defects in staining are due to lack of familiarity with the conditions which must be controlled in order to produce satisfactory stains, just as it was in our case before we began this study

## CONDITIONS WHICH MUST BE CONTROLLED

### I *In regard to the blood smear*

#### I Glassware. (Must be free

from acid, alkali, grease, and dirt)

- 2 Thickness of Blood Smear (Too thick—crenation during drying, poor fixation with methyl alcohol of stain)

### II *In regard to the stain itself*

- 1 Quality of pigment
- 2 Concentration of pigment in staining solution (Too concentrated—overstains red, too dilute—understains)
- 3 Quality of alcohol (Unless almost 99%, red cells are poorly fixed—distorted and vacuolated)
- 4 Quality of water (Acid water—stain too red, alkaline water—too blue, impurities—precipitated stain)
- 5 Proportion of water to stain (Too little water—precipitated stain, too much—understaining)
- 6 Staining time (Usually varies with each new batch prepared)

### III *In regard to personal factors*

- I Due to forgetfulness or distractions

\*Presented before the American College of Physicians at the Annual Clinical Session, March 8, 1928, New Orleans, La



stand until stain remaining *turns red*

- 2 Cover slide with buffered water, let stand for one minute or longer
- 3 Wash with Solution II until most of the red precipitate on the slide disappears
- 4 Wash with buffered water, dry, and examine

A little experience with this new procedure will demonstrate that a number of the errors due to personal factors are eliminated. In the first place, drying at any stage *after draining off excess stain* does not materially harm the preparation, which in itself is a marked advantage. Forgetfulness and distraction are much less likely to result in ruining smears, since they can be left standing almost indefinitely at any point in the procedure and the stain completed when you come back. Likewise there is less opportunity for bungling and accidents to play a part. No doubt all of you have had your Wright's stain run off over the edge of your slide, and continue to do so even when you add more, which completely upsets your calculations as to how much water should be added, and also usually means that a part of the slide has had the stain dry on it before the minute of application has passed. Moreover, I am sure that everyone has experienced difficulty in getting the diluting water to spread rapidly over the slide in staining by the usual procedure, and any part not covered by water almost immediately will be covered with precipitated stain. These difficulties are avoided in the new procedure.

In our experience, and in that of others who have been kind enough to test out our procedure, much more uniform results are obtainable, not only because of the minimizing of the influence of personal factors, but also because of certain inherent advantages in the procedure itself. The staining time is of considerably less importance. Nuclei are almost as deeply stained within one minute after the water is added as in longer times. Less than a minute, however, usually fails to stain sufficiently.

The proportion of water to stain has no influence, since an excess is always added.

There is no overstaining of preparations, as all excess stain is removed by Solution II.

It is likewise of considerable interest to note that the control of a few major factors assures great constancy in staining. Taking it for granted that those who stain blood smears can prepare good thin smears on properly cleaned glassware, we believe that the proper control of four major factors will insure uniformity.

The first factor, and one of the most important ones, is the reaction of the water used. Using water buffered with phosphate solutions we find that the colors which we prefer are obtained when the water is a pH of 6.4 to 6.8. The colors are fairly satisfactory for differential counting with a pH as low as 5.6, but the erythrocytes are very pink and the nuclear blues of the leucocytes are hazy and indistinct. On the other hand, when the pH goes beyond 7.4 the red cells

take on a greenish blue hue and the granules and nuclei of the leucocytes fail to take the eosin and azure properly

Distilled water is usually slightly acid and consequently makes a satisfactory diluting and washing medium without buffering. However, the amount of acid is subject to variation, especially where the water is distilled from city supplies which are chemically treated. For this reason we prefer to use a water which is buffered.

A simple method of preparing such a water is to keep on hand 1% solutions of  $\text{KH}_2\text{PO}_4$  and  $\text{Na}_2\text{HPO}_4$ . Usually 30 c.c. of the former and 20 c.c. of the latter added to a liter of distilled water will give about the proper reaction. If the erythrocytes stain too pink more of the sodium phosphate can be added, if not pink enough, more of the potassium is added.

A second important factor to be controlled is the percentage of ethyl alcohol used in preparing Solution II. The best strength is 85-90%. Stronger alcohol often fails to remove the red precipitate left in overstaining the smear and also tends to make the erythrocytes pinker. Weaker alcohol removes both reds and blues, even to complete decolorization.

A third factor is the concentration of the pigment in Solution I. It often happens that a stain loses considerable alcohol by evaporation, thereby becoming concentrated. Such a solution will cause overstaining with eosin. On the other hand, too dilute a solution will cause understaining or bluish color to predominate.

The fourth factor is the staining time, which, though of less importance than in the usual procedure, must be controlled within certain rather wide limits. Less than a minute of staining after the addition of water usually means understaining, while an exceedingly long time will cause an overstaining with red.

Every method will have certain points which some will consider disadvantages, and this is true of this procedure. One point is that there are two solutions, instead of one, to be prepared and used, and this is a fairly large objection in the minds of some.

Another is that thinner smears must be used on account of the short exposure of the preparation to the methyl alcohol of Solution I, which is not sufficient for proper fixation of the erythrocytes in thick smears.

A third point is the fact that the stains obtained are much more delicate. Those used to the dense and opaque nuclei often resulting from slight overstaining by the usual procedure depreciate the more delicate colors of the nuclei and granules of the leucocytes. Personally we prefer the colors obtained by this procedure because we feel that we can see more structure in the cells and the differentiation of the various kinds of leucocytes is as clear-cut, if not more so, than with the ordinary Wright's stain.

Not only do we feel that normal structures are well delineated but pathological conditions are also well demonstrated. The delicate tints of the erythrocytes bring out clearly the basophilic stippling occurring in the various anemias and also the poly-

## Variable Factors in the Use of the Wright's Stain

chromatophilia or diffuse bluish staining of certain red cells usually accompanying the stippling

Malarial parasites are beautifully stained, and the various structures are distinctly discernable. Schueffner's dots show up very plainly in tertian malaria.

The pathological leucocytes and erythrocytes of the anemias and leukemias are also well differentiated, the granules of the various myelocytes taking on very characteristic colors.

A very convenient summary of this study will be to rearrange the points discussed into an outline for eliminating defects in staining with the two solution Wright's Stain. It follows:

### *I Intercellular or Pericellular Stain (Bluish or Pink)*

- 1 Improperly washed slides
- 2 Too concentrated Solution I
- 3 Too short application, or uneven application, of Solution II

### *II Granular Precipitate Over Smear*

- 1 Granules of dried stain from mouth of staining bottle
- 2 Allowing stain to evaporate before draining off excess
- 3 Improperly washed slides

### *III Predominance of Red*

- 1 Water too acid
- 2 Solution I too concentrated
- 3 Solution II made with 90% or higher, ethyl alcohol
- 4 Staining time too long
- 5 Pigment contains too much eosin

### *IV Predominance of Blue*

- 1 Water too alkaline
- 2 Solution not concentrated enough
- 3 Solution II made with less than 85% ethyl alcohol
- 4 Staining time too short
- 5 Pigment contains too much polychromed methylene blue
- 6 Smears too old (Over a week old—difficult to stain)

### *V Stain Pale*

- 1 Staining time too short
- 2 Solution I not concentrated enough
- 3 Solution II not saturated with pigment

### *VI Vacuolated or Distorted Erythrocytes*

- 1 Smears too thick
- 2 Smears dried too rapidly
- 3 Methyl alcohol (Solution I) contains too much water



# Editorial

## *POSSIBLE RELATIONSHIPS BETWEEN PAROTID AND PANCREAS*

Because of certain anatomical and physiological similarities between the salivary glands and the pancreas, as well as the common involvement of both organs in certain affections, there has long existed a well-defined scientific curiosity as to the possibility of functional inter-relationship between them. As early as 1890 the Italian school based such a belief upon the work of De Renzi and Reale who had demonstrated experimentally the occurrence of glycosuria in dogs after the removal of the duodenum and the salivary glands, the pancreas being left in the body. These workers concluded that the salivary glands had a specific function aside from the production of saliva. This view was opposed by Minkowski who regarded the glycosuria in this experiment as a transitory one, and not comparable in degree to that shown by him to follow the total extirpation of the dog's pancreas. Nevertheless, numerous writers felt that the question was still an open one, and the idea persisted that there might be other organs or tissues concerned in the sugar metabolism besides the pancreas. If such were true, then these other organs might compensate for the pancreas when its function was lowered. In 1893, A. Seelig advanced the hypothesis that by

gradual suppression of the pancreatic function glycosuria might not take place because of the compensatory activities of other organs. In 1906, another Italian worker, Italia by name, demonstrated the occurrence of parotid hypertrophy following experimental atrophy of the pancreas, as well as the reverse production of pancreatic hypertrophy following experimental extirpation of the salivary glands. Recently this question has been attacked anew from an entirely different angle, that of blood-sugar estimations, and during the last year a number of investigators in different parts of the world have been working independently along this line, and have come to similar conclusions. Goljanitska and Snairnowa have attempted the surgical treatment of diabetes by parotid ligation and transplantation of portions of the submaxillary gland. They ascribed a definite therapeutic result to this surgical method. Utimura found that extirpation of the parotid glands in dogs led to a permanent lowering of the blood-sugar, followed by a gradual numerical increase in the islands of Langerhans in the pancreas, and an increase of the glycogen content of the liver parenchyma. This same investigator found also that there existed an antagonistic relationship of the submaxillary gland towards the parotid. Mansfield also found that the experimental

cutting out of the parotid by means of the ligation of Stensen's duct produced the same depressant effect upon the blood-sugar of the dog. More recently S. Seelig has reported the results of similar experimental work as to the effect upon the blood-sugar of dogs by the suppression of the external secretion of the parotid. He first investigated the effects of parotid ligature upon the hyperglycemia of dogs with pancreatic diabetes, and found that the suppression of the external secretion of the parotid had no effect upon the hyperglycemia in the dog following total pancreas extirpation, the animals died with the characteristic diabetes cachexia. A second series of experiments was then carried out in which after a preliminary proving of the fasting blood-sugar for a number of days, the parotid duct was first ligated, and then after several days the total extirpation of the pancreas was carried out. From this series of experiments it appeared that the total extirpation of the pancreas following parotid ligature did not lead to such high blood-sugar values, as when it is carried out without parotid ligation. Further, the dogs showed a better healing of the wounds, and did not develop the characteristic rapidly progressive cachexia of pancreatic diabetes. Another series of investigations was concerned with the study of the fasting blood-sugar in dogs in whose Stensen's duct alone had been ligated. The state of the blood-sugar was observed, and the functional regulation tried out by the administration of adrenalin and glucose. Following the operation there developed in one to two days a stasis-tumor

of the cheeks which declined after five or six days. The animals showed a marked hunger, rapid loss of weight and fatigability. The testing of the blood-sugar regulating function by means of adrenalin and glucose showed a slight hyperglycemia in the dogs with parotid ligatures, as well as in dogs not so treated. Insulin susceptibility was also tested, the convulsion threshold was found to be lower in the ligated dogs than in normal animals. The functional proving was not, however, carried out in a sufficiently large number of animals, and the author offers these results with reservations. The histological study of the parotid, liver and pancreas of these cases was also not completed, and will be reported later. Since January, 1928, ten diabetic patients have been treated by means of parotid duct ligation in Sauerbruch's clinic, by means of a special technic devised by Gohrbandt. They were in part moderately severe cases and in part severe. It is yet too soon to speak definitely of the results in these cases. Seven appear to have been favorably influenced as far as the symptoms of blood-sugar, urine-sugar, acidosis and furunculosis were concerned. Three cases remain unaffected, they will be reported upon later. It should not be necessary to state that this operation is only in the experimental stage, and should not at this time be regarded as having a general application in the therapeutics of diabetes mellitus. The final conclusions and judgment of the results of this operation will be given in a later publication. At the present time any judgment as to the practical value of this work must be withheld.

The results of these different investigations as to a possible functional relationship between the parotid and pancreas are extremely interesting. They serve to support the old ideas promulgated by the Italian workers of the last decade of the last century, and various clinical surmises that have since been made. Many interesting observations have been reported from time to time of pancreatic involvement in epidemic parotitis. Acidosis and glycosuria have been observed to occur at the peak of an attack of mumps, and the question arises as to whether these symptoms are due directly to the disturbed function of parotid and submaxillary glands or to autoinfection of the pancreas with consequent functional disturbance. A number of writers have emphasized the not infrequent complication in mumps of a benign form of pancreatitis with symptoms of abdominal pain, vomiting and palpable pancreatic tumor. Sugar may appear in the urine, and some cases of well-defined diabetes have been thought to have their origin in a pancreatitis complicating mumps. There are, therefore, a number of recorded observations bearing upon the question of parotid and pancreas interrelationships, recent experimental work seems to be drawing these towards a focusing point. Further experimental work along this line will be awaited with great interest.

#### *HEALTH OF WORKERS IN DUSTY TRADES*

The United States Public Health Service has completed a study of the

health of workers in a Portland cement plant, the first of a series covering the dusty trades, according to an announcement recently made by Surgeon General H. S. Cumming. The study was undertaken to ascertain whether persons working in an atmosphere containing numerous minute particles of a calcium dust suffered any harmful effects. The investigation was conducted in one of the older, dustier plants, so that the effect of large quantities of the dust could be observed. Records of all absences from work were kept for three years, and the nature of disabling sickness was ascertained. Physical examinations were made, X-ray films taken, and the character and amounts of dust in the atmosphere of the plant were determined.

The results of this investigation indicated that the calcium dusts generated in the process of manufacturing Portland cement do not predispose workers to tuberculosis nor to pneumonia. The workers exposed to dust experienced, however, an abnormal number of attacks of diseases of the upper respiratory tract, especially colds, acute bronchitis, diseases of the pharynx and tonsils, and also influenza or grippe. Attacks of these diseases serious enough to cause absence for two consecutive working days or longer occurred among the men in the dustier departments at a rate which was about 60 per cent above that of the men in the comparatively non-dusty departments. Limestone dust appeared to be slightly more deleterious in this respect than cement dust.

Outdoor work in all kinds of weather such as was experienced by the

quarry workers appeared to predispose to diseases of the upper respiratory tract even more than did exposure to the calcium dusts. In the outdoor departments of the plant, also, the highest attack rates of rheumatism were found. The study also indicated that work in a cement dusty atmosphere may predispose to certain skin diseases such as boils, to conjunctivitis, and to deafness when cement dust in combination with ear wax forms plugs in the external ear. When the dust in the atmosphere is less than about ten million particles per cubic foot of air it is doubtful that the above-mentioned diseases and conditions would be found at greater than average frequency.

Modernization of plants and installation of ventilating systems are helping to solve the dust problem of the industry.

#### *PUBLIC HEALTH IN FLOODED AREA OF MISSISSIPPI VALLEY*

Approximately one year has elapsed since the frightful disaster of the

flood in the Mississippi Valley. The United States Public Health Service states that some comfort may be obtained in the knowledge that better communities are being builded on the ruins of those destroyed, and as a rule, a better public health regime has been inaugurated. Following the flood of waters there has developed another flood—a flood of sanitation development, which has placed that area many years ahead of the old program in connection with the development of full-time county health service. Since July, 1927, 78 counties have joined the roll of those that are enjoying adequate public health protection through the labors of over 300 full-time health workers. This is a distinct step forward, and a stimulus to perpetuate these endeavors.

If the work continues as it has to date, the Mississippi Valley will soon enjoy the universal public health protection it deserves.

This should serve as a splendid example to other communities and stimulate them to strengthen their local health departments and secure adequate full-time health service.

## Abstracts

### *Emetin—Its Effect on the Rabbit's Heart*

By PHOEBUS BIRMAN and WILLIAM H LEFKI, (Research Prize Essay of the California Medical Association for 1928 California and Western Medicine, June, 1928, Vol XXVIII)

Myocardial failure associated with the therapeutic use of emetin is not unknown, and probably occurs more frequently than the reports indicate, as emetin and its salts are widely used in the treatment of amebiasis and other protozoan infections. The literature contains only a few articles dealing with the effects of emetin on the heart. It was thought, therefore, that an electrocardiographic study of the effect of emetin on the rabbit's heart might reveal interesting findings. Such an investigation was carried out, with the following results. In rabbits, emetin hydrochlorid given intravenously in doses between one and two mg per pound body weight will produce a distinct ventricular tachycardia which will revert to a normal rhythm in about ten minutes. Digitalis in the form of digifolin will produce no definite change in the electrocardiogram of a rabbit when administered intravenously in very large doses. Emetin hydrochlorid given in conjunction with a relatively small amount of digitalis (digifolin 1 cc) will not produce a definite change in the electrocardiogram unless the dose of emetin is between one and two mg per pound body weight. In other words, digitalis will not lessen the dose of emetin required to produce definite changes in the electrocardiographic record. The minimal intravenous lethal dose of emetin hydrochlorid for a rabbit is about 2 mg per pound body weight. The electrocardiogram of a rabbit receiving a lethal dose of emetin hydrochlorid shows a ventricular fibrillation from which, in their experiments, the ani-

mals did not recover. Daily intravenous injections of emetin hydrochlorid approximately equivalent to 1 mg per pound body weight produce no marked permanent changes in the electrocardiogram of rabbits receiving a total amount of 18 mg and 28 mg respectively. An electrocardiogram of a rabbit dying of sodium cyanid is given for purposes of comparison.

### *An Investigation to Determine a Satisfactory Standard for Beriberi-Preventing Rices* By EDWARD B VEDDER and T R FELICIANO (The Philippine Journal of Science, April, 1928, p 351)

Although medical authorities still differ with regard to a number of details concerning the etiology of beriberi, there is a very general consensus of opinion to the effect that beriberi is a deficiency disease, produced whenever, in the absence of an adequate mixed diet, highly milled rice is used as the main food staple, and that the disease can be prevented by the substitution of a sufficiently undermilled rice. In the case of the Philippine Scouts, when supplied with the best grade of highly milled rice, during the years 1902-1909, the incidence of beriberi was often as high as 10 per cent of the entire number (5,000). Since 1910, when undermilled rice was substituted, beriberi has been eradicated among these troupes, although they were living in the midst of a population where beriberi is very common. Such experiences led several sanitary authorities to recommend legislation by the various countries most concerned which would diminish the production or importation of highly milled rice, but it was promptly realized that no such law could be administered without a satisfactory legal standard for beriberi-preventing rices. Beriberi cannot be eradicated without legis-

lation in the countries in which it is endemic, and legislation waits on the determination of a satisfactory standard for beriberi-preventing rices. Accordingly this investigation was begun in 1925, and completed in 1927, and the following conclusions were drawn. The chemical index proposed for beriberi-preventing rices is Any rice having 1.77 per cent of phosphorus pentoxide plus fat, but not less than 0.4 per cent phosphorus pentoxide, or any rice having not less than 0.62 per cent phosphorous pentoxide and with at least 75 per cent of the external layers of the grain remaining. No rice possessing these requirements was found to produce polyneuritis in pigeons, and this standard excluded only nine rices out of two hundred that afforded protection to pigeons. Since pigeons are so much more susceptible to the deficiency of anti-neuritis vitamin than is man, and since man seldom lives on rice alone, a standard that will protect pigeons will not only protect man, but will also provide a factor of safety. This factor of safety is a necessity if beriberi is to be eradicated, because defects in the storage of rice or in its preparation for food may materially reduce its vitamin content. Of ten rice samples tested, thorough washing reduced the phosphorus pentoxide content from an average of 0.447 to an average of 0.197 per cent. Presumably the vitamin content was similarly reduced. In an experiment with twenty insect-infested rices stored for one hundred days, an average total of 2.61 per cent (fats phosphorous pentoxide and ash) was reduced to 1.71, and seven undermilled rices that should have prevented polyneuritis were converted into highly milled rices that produced polyneuritis. It is, therefore, highly probably that the loss of vitamin during long storage of undermilled rice is caused by the depredations of insects that eat the external layers of the grain.

*Zur Frage der toxischen Synthalin-Wirkung bei diabetischen Kinder.* By H. HIRSCH-KAUFFMANN and A. HEIMANN-FROSTEN (Klinische Wochenschrift, July 1, 1928, p. 1272.)

Fifteen diabetic children have been treated systematically with synthalin for over a year, and it has, therefore, been possible to make a more accurate judgment as to the effect upon the carbohydrate tolerance of the peroral use of this anti-diabetic remedy and as to the toxic effect upon the child's organism of its protracted use. As these writers have previously emphasized, an effective synthalin therapy is possible only by correct dosage more than one and a half mg. of synthalin per kilogram body-weight must not be given, they advise one mg. per kilogram body weight. Higher dosages produced constantly bad results. A pure synthalin therapy is possible only with patients whose glycosuria is not too high (20-30 g.). In such cases it has been possible to treat children six to twelve years of age for a year without insulin on the mixed diet recommended previously by these authors, not only in the Clinic but also ambulatory cases. The children attended school and showed normal development, both as to weight and increase in height. No permanent injury resulting from the treatment was observed. The temporary appearance of slight glycosurias as the result of infections lowering the tolerance could not, however, be avoided by the synthalin treatment. While in such cases treated by insulin it is possible by careful increase of the dose to control the glycosuria, it is not possible to do this with synthalin because of the production of unpleasant symptoms, such as loss of appetite, vomiting, etc. Under such circumstances, as in the pre-insulin period, the child must be brought into a metabolic equilibrium by a temporary limitation of the diet, especially of the carbohydrates. In this way the authors were able to bring their diabetic children through mild colds, otitis, and even a more severe epidemic of mumps. It was observed also that synthalin treatment produced an insulin resistance, so that larger doses of the latter were needed to produce an aglycosuria. This resistance is apparently relative, since in further treatment with insulin the dose could be reduced. It is also possible that the use of synthalin makes larger quantities of car-

bohydrates utilizable to the organism, so that after its discontinuance larger doses of insulin are required to meet this increased utilization. As to toxic effects produced by this guanidin preparation, occasional vomiting, temporary loss of appetite, and abdominal pains were the only symptoms observed, these were not serious and disappeared spontaneously. In one case icterus appeared and the synthalin treatment was discontinued. The significance of this case could not be determined. It has been assumed that synthalin had an injurious effect on the liver, on the other hand icterus is not a rare complication of diabetes, or it may have been an ordinary catarrhal jaundice. In both insulin- and synthalin-treated cases of diabetes there is an occasional urobilinuria, but no striking increase of icterus in the synthalin-treated cases has been observed. The authors do not regard their case as indicating a hepatic injury due to the treatment, the child quickly recovered and gained three pounds in weight, so that there could have been no permanent liver damage. They conclude from their year's experience with this drug that synthalin aids in the treatment of diabetes in children. Even though it cannot completely replace insulin, it works especially well in combination with insulin. With its use the need for insulin is so lowered that one injection daily of the latter may suffice, in this way a great saving of insulin is effected. Of greater importance is the fact that with synthalin treatment hypoglycemic reactions, the most unpleasant results of insulin treatment, occur much less frequently as the result of the combination therapy. There are juvenile diabetics whose daily needs for insulin vary so greatly, that in spite of the most extreme precautions there may be multiple occurrences of hypoglycemia in a single week. For such cases synthalin becomes an adjunct of greatest service. Since synthalin does not wholly meet the therapeutic requirements scientific investigations must be continued until some preparation is produced whose use will be unattended by symptoms, and the necessary doses of which can be given to

any diabetic without consideration of possible harmful results.

*Zur Pathogenese der gastrogenen Tetanie*  
By HERMANN STRINITZ (Klin Wochenschr, May, 1928, p 932)

Gastrogenous tetany is a rare disease. In the cases that have been observed throughout the world many causes have been advanced in its explanation. These may be divided into five groups: concentration of blood due to loss of water, reflex action, autointoxication, loss of chloride, and alkalosis. In the last few years the discussion has limited itself more and more to the three last named hypotheses. During a short period recently two cases of typical gastrogenous tetany were observed in the Strauss Clinic in Berlin. One of these was a case of pylorus stenosis caused by a parapyloric ulcer, the other a low lying duodenal stenosis due to a carcinoma of the duodenojejunal flexure. In both of these cases the blood studies showed a normal refraction index towards the upper limit of a slightly increased one, a normal potassium and calcium picture, a negative N balance in one case, and a slightly increased residual N value in the other, extreme high values for the alkali reserve, very low blood-chloride and almost chloride-free urine, marked chloride retention, a lowering of the formerly hyperacid stomach contents to an acidity with very low chloride values. In both cases the extremely low chloride deficiency of the organism, due to the excessive vomiting, appeared to be the decisive, at least the exciting factor, in the origin of the tetanic phenomena. Certainly in these two cases the loss of chloride appeared to be of essential significance for the occurrence of gastrogenous tetany. The question naturally arises as to the mechanism operating in these cases. Only a relatively small number of cases of pyloric stenosis develop tetany. Why does tetany practically never develop in association with the pylorus spasm of infants, although the same symptoms of acid vomiting, hyperchloremia, hypercapnia, partly decompensated alkalosis, etc., occur in this condition, as in the case of pylorus stenosis in adults? It ap-

pears that something more is necessary—a certain disposition—in the form of tissue- or blood-changes of a tetanogenic character. Changes in the parathyroids are at once suggested. The experimental and postoperative parathyreoprival tetany is, of course, well known, but for other forms of tetany parathyroid changes and their significance are still disputed. In some cases of gastrogenous tetany anatomical changes in the parathyroids have been demonstrated, in other cases, as in the two of Steinitz, no such changes are found. Such negative findings do not, however, exclude the pos-

sibility of functional changes. In one of Steinitz's patients "softening and crumbling" of the teeth had been noted at puberty coincident with the beginning of stomach symptoms, this might be an indication of parathyroid insufficiency. It is well known that such a disturbance may be for a long time latent, until brought to manifestation through toxic irritation or a change in the ionic equilibrium. It is possible that gastrogenous tetany is a relative parathyroid insufficiency, whereby the chloride loss becomes the exciting moment for the production of tetany.



## Reviews

### *Modern Medicine Its Theory and Practice*

In Original Contributions by American and Foreign Authors Edited by SIR WILLIAM OSLER, Bart, M.D., F.R.S. Third Edition, Thoroughly Revised. Re-edited by Thomas McCrae, M.D., Professor of Medicine in the Jefferson Medical College, Philadelphia, Fellow of the Royal College of Physicians, London, Formerly Associate Professor of Medicine, The Johns Hopkins University. Assisted by Elmer H. Funk, M.D., Clinical Professor of Medicine, Jefferson Medical College, Philadelphia. Vol. VI, Diseases of the Nervous System—Diseases and Abnormalities of the Mind. 964 pages, illustrated. Lea and Febiger, Philadelphia, 1928. Price in cloth, \$9.00.

This is the final volume of the third edition. Its contributors include Barker, Spiller, Russel, Bramwell, Collins, Cushing, Hunt, Thomas, Taylor, Holmes, Buzzard, Clark, Burr, Jelliffe, McCarthy, Sachs and Strecker. The contents consist of two parts, the first on Diseases of the Nervous System, the second on the Diseases and Abnormalities of the Mind. Part II is written wholly by Edward A. Strecker, while the other authors mentioned above have collaborated on Part I. The introduction is by Barker, diseases of the motor system by Spiller, combined diseases of the spinal cord by C. K. Russel, sclerosis of the brain and diseases of the meninges by Edwin Bramwell. Joseph Collins has written the sections on topical diagnosis of diseases of the brain and aplasia, Harvey Cushing those on intracranial tumors and hydrocephalus. Ramsay Hunt has revised Southard's chapter on acute encephalitis and brain abscess and written the one on epidemic encephalitis. Henry M. Thomas, Jr., has revised the section on diseases of the cerebral bloodvessels. The chapter on diseases of the cerebral

nerves has been written by E. W. Taylor and that on the peripheral nerves by G. M. Holmes. The diffuse and focal diseases of the spinal cord is by Buzzard and Symonds of London. L. P. Clark is the contributor of the section on epilepsy and C. W. Burr of that on the traumatic neuroses and psychoses. The two sections on hysteria, the migraines, neuralgia, professional spasms, occupation neuroses and tetany are by Smith E. Jelliffe. The three sections including paralysis agitans, chorea, choreiform affections, infantile convulsions, myasthenia gravis, paramyoclonus multiplex, periodic paralysis, astasia-abasia and adiposis dolorosa are by Daniel J. McCarthy. Syphilitic diseases of the central nervous system and amaurotic family idiocy are contributed by B. Sachs. This volume seems to the reviewer to be the best one of the third edition. It is well brought up to date, and includes good presentations of modern views of the diseases of the central nervous system. In itself this volume constitutes an excellent textbook on diseases of the nervous system, and it is especially adapted to the uses of the internist who will find in it our knowledge of this subject so arranged that it will answer his immediate clinical needs in diagnosis.

*Modern Methods of Treatment* By LOGAN CLENDENING, M.D., Associate Professor of Medicine, Lecturer on Therapeutics, Medical Department of the University of Kansas, Attending Physician, Kansas City General Hospital, Physician to St. Luke's Hospital, Kansas City, Missouri. With chapters on Special Subjects by H. C. Anderson, J. B. Cowherd, H. P. Kuhn, Carl O. Rickter, F. C. Neff, E. H. Skinner and E. R. DeWeese. Second Edition. 815 pages, 96 illustrations. The C. V. Mosby Company, St. Louis, 1928. Price in cloth, \$10.00.

The many changes in therapeutics of the last five years have made the revision of this book necessary. The Minot-Murphy diet in pernicious anemia, the scarlet fever antitoxin, the parathyroid hormone, the ovarian hormone, ephedrine sulphate, novarsol and ammonium chloride in edema, the malarial treatment of syphilis, lipiodol instillations in chronic lower respiratory infections, the metabolism of obesity, spirochetal pulmonary infections, the use of peptone in migraine, phenylhydrazine in polycythemia, etc., have necessitated the addition of much new material. The author has also added new sections on antidotes and the treatment of acute poisonings, resuscitation by artificial respiration, and new chapters on the treatment of the chronic intoxications, of the diseases of the organs of locomotion, and of the common diseases of the nervous system. The entire book has been carefully revised. Particularly the chapters on Digitalis, Asthma and Diabetes have been recast. The tenth edition of the Pharmacopeia has been used as a basis for revision of drug nomenclature. About twenty-five new illustrations have been added. The general plan and purpose of the book have not been changed. The author has kept the general practitioner in mind and has endeavored to encourage him to adopt and to use methods which he is likely to believe are effective only in the hands of specialists. There is a large amount of valuable material in this book, but also a large number of methods of treatment so incompletely described that they cannot be of much use to the practitioner. Some of these read as if they were seen only in abstracts, and not in the original article. Take the liver treatment of pernicious anemia, the preparation of liver, amount to be taken, etc., are given, but no word of the regulation of the treatment according to the blood changes, and there is no mention of liver-extract which has been used for over a year. This incompleteness of detail is true of other remedies and treatments advocated. It is not sufficient to mention a therapeutic agent, and to give dosage and possible results. What the practitioner needs are the details of treatment indicating the results, the dangers, and the after-effects.

It seems to the reviewer that the book is somewhat lacking in this respect.

*The Glands of Destiny*. A Study of the Personality. By Ivo GEIKIE COBB, M. D., 295 pages. The MacMillan Company, New York, 1928. Price in cloth, \$3.00.

This is an attempt to express in a popular style the role of the endocrine glands in the formation of the individual personality. As the author states it, what is herein discussed may be called the physical or chemical contribution to the personality, in which contribution the glands of internal secretion play a chief part. The personal equation is determined in part by tangible causes, and in part by other factors more or less abstract. While there are still many gaps in our knowledge of these structures and their functions, enough is now known to warrant a survey of their relationship to that psychological mixture known as the personality. The author realizes the danger in doing this, and hopes that surmise has not outrun its legitimate course in his book. He has attempted to distinguish physiologic facts from assumptions based thereon. After an introductory general discussion of the endocrine glands he takes up each one in turn giving a brief and concise account of what is known of their function and interactions, and the human types associated with pathologic conditions of these glands. Upon this foundation he constructs various hypothetical applications to racial characteristics, the process of aging, civilization and warfare, the internal secretions in everyday life and personality. The author has been unable to resist the temptation to make a little stronger case for his hypotheses than the actually known facts warrant, and the danger is that a non-medical reader may take it all as absolute fact, which it is not. Perhaps this is offset by the important ideas that he will acquire by its perusal.

*Syphilis. A Treatise on Etiology, Pathology, Symptomatology, Diagnosis, Prognosis, Prophylaxis and Treatment*. By HENRY H. HAZEN, A. M., M. D., Professor of Dermatology and Syphilology, Medical Department of Georgetown Uni-

versity, Professor of Dermatology and Syphilology, Medical Department of Harvard University; Visiting Dermatologist to Georgetown University Hospital, Freedmen's Hospital. Second Edition. 613 pages, 165 illustrations, including 16 figures in color. The C. V. Mosby Company, St. Louis, 1928. Price in cloth, \$10.00.

This is the best of the smaller textbooks on syphilis, in that it is brought up to date in the modern knowledge of syphilis, and speaks from an acquaintance with recent literature. It is therefore authoritative. It is not made up of old statements handed down from textbook to textbook for the last fifty years, but presents a thorough and careful analysis of what we have learned of syphilis since the discovery of the spirochete. This enormous mass of information is condensed into a very readable text. Authorities are mentioned with a reference number in the text, and at the end of each section the full reference in the literature is given. This makes the work an exceedingly useful one for the medical student, who can comprehend easily the pithy résumé of the subject, and then be able to look up the original investigations mentioned since the full references are at hand. In many respects the second edition is practically a new book. The chapters on Occurrence and Economic Importance, Syphilis of the Nervous System, Diagnosis, Prophylaxis and Treatment have been entirely rewritten. All of the remaining chapters have been revised, and the most recent bibliography added. New illustrations have been added. These illustrations in general are very good and give a good idea of what they are intended to represent. Many of them are of special interest in showing the character of syphilitic lesions in the colored race. Taking it all in all this book gives an excellent treatment of syphilis within its limitations of size, and it can be relied upon for an accurate statement of the most essential facts concerning syphilis.

*Diathermy Its Production and Uses in Medicine and Surgery* By ELKIN P. CUMBLERBATCH, M. A., B. M. (Oxon.), D.

M. R. I. (Camb.), M. R. C. P., Medical Officer in Charge, Electrical Department, St. Bartholomew's Hospital, etc., Examiner in Medical Electrolgy, University of Cambridge, Former President, Section of Electrotherapeutics, Royal Society of Medicine. Second edition. 332 pages, 87 illustrations. The C. V. Mosby Company, St. Louis, 1928. Price in cloth, \$7.00.

The progress made in recent years in the medical and surgical uses of diathermy, and in the design of apparatus has rendered necessary a complete revision of the first edition and a considerable addition to its size. At the time when that book was written the field of diathermo-therapy had not been widely explored, and it was necessary to advocate much caution in the treatment and to limit the diseases for which it could be safely prescribed. Now, however, the gain of knowledge and experience has confirmed the value of diathermy in the diseases for which it was recommended and established its usefulness in the treatment of other diseases. This has been particularly the case in many of the diseases peculiar to women and in others due to gonococcal infection. The results of the experience gained in the past six years in the Electrical Department of St. Bartholomew's Hospital have been incorporated in the present edition. The parts dealing with the surgical uses of diathermy have been enlarged and almost wholly rewritten, and an introductory account of the new "cutting currents" has been added. The contents of the book include an introduction, historical note, high-frequency currents, the original high frequency generator, the production of currents yielding higher degrees of diathermy, the diathermy machine, the path and distribution of the diathermy current in various conductors, the degree and distribution of heat produced by the diathermy current, the action of diathermy in health, medical diathermy and the use of high-frequency currents in surgery. These chapters discuss very fully the technical side of diathermy and its practical applications in medicine and surgery. It is written simply and succinctly, without undue enthusiasm or exaggeration. The general principles and

theory of diathermotherapy can be easily understood and acquired through this book

*Nurses Patients and Pocketbooks* Report of the Economics of Nursing Conducted by the Committee on the Grading of Nursing Schools. By MAY AARIS BURCISS, Director. 618 pages, 70 tables and 61 diagrams. Published by the Committee, 370 Seventh Avenue, New York, 1928. Price, \$2.00

This is an important economic study made by the Committee on the Grading of Nursing Schools covering its complete findings in its two years study of supply and demand in nursing service. It is founded upon 31,000 returns from nurses, 28,000 returns from physicians, 3,400 returns from hospitals, and 3,200 returns from patients, registrars, etc., in all parts of the country. Dr. William Darrach was the Chairman of

this Committee. The data for this book were gathered chiefly through 19 questionnaires, 343,772 of which were sent out, and at the time of publication 67,938 of which had been returned, and additional returns were still being received daily. The text of these questionnaires is contained in the Appendix. The discussion and summary of the important results of this study are beyond the possible limits of a review, and we intend to present these later in an editorial on this subject. Suffice it to say at present that the facts secured have great economic significance to practical medicine, both educational and hospital and private practice. The striking development of the relationship between the nursing profession and the medical profession since 1900 must call for careful thought and consideration by the members of both professions, from the economic aspects alone if from no other. This report should be read by all thoughtful practitioners of medicine.

## College News Notes

Dr Arthur C Morgan (Fellow), Philadelphia, Pa, and Dr Thomas G Simonton (Associate), Pittsburgh, Pa, were speakers at the Seventh Councilor District Meeting of the Medical Society of the State of Pennsylvania at Williamsport on July 13. Dr Morgan and Dr Simonton are respectively President and President-Elect of the State Medical Society.

Dr George F Pfahler (Fellow), Philadelphia, attended the International Conference on Cancer in London, July 16-22. He also attended the International Congress on Radiology at Stockholm, Sweden, July 23, representing various American radiological societies and the faculty of the Graduate School of Medicine of the University of Pennsylvania.

Dr Harry Piercy (Fellow), Cleveland, Ohio, served as Secretary and Treasurer of the Western Reserve University Medical Alumni Association from 1919 to 1927 and as President of the same organization from 1927 to 1928, was re-elected President for the ensuing year at the annual meeting of the Association at Cleveland on June 12.

Dr Oliver T Osborne (Fellow, and Governor for Connecticut), New Haven, Conn, was recently made an honorary member of the American Medical Editors Association, which Association has recently been organized with Dr H Lyons Hunt, New York, as President. Dr Osborne has been placed on the Committee on Pharmacology and Therapeutics.

Dr Rollin H Stevens (Fellow) and Dr Hans A Jarre, both of Detroit, Mich, have recently announced the association of Dr Clyde K Hasley, former instructor in Dermatology and Roentgenology at the University of Michigan. Drs Stevens, Jarre and

Hasley will limit their practice to X-Ray Diagnosis, Dermatology, Radium and X Ray Therapy.

Dr Samuel E Munson (Fellow), Springfield, Ill, addressed the DeWitt County Medical Society on June 22 on the subject "Cardiac Lesions". Dr Munson represents the State of Illinois on the Board of Governors of The American College of Physicians.

Dr E Bosworth McCready (Fellow), Pittsburgh, Pa, was elected president of the American Therapeutic Society for 1928-29 at the meeting of that Society at Minneapolis, June 9 to 11.

Dr A B Olsen (Fellow), Battle Creek, during the fall of 1927, visited a number of European hospitals and clinics with a special view to observing and studying Epidemic Encephalitis. Last spring he delivered a paper entitled "Some Thoughts on Epidemic Encephalitis Gathered from a Recent Visit to European Hospitals" before the Detroit Neurological and Psychiatric Society, and this paper was later published in full in the Michigan State Medical Society Journal for June.

At the meeting of the American Medical Association at Minneapolis in June, Dr Olsen read a paper on "The Effect of Liquid Petrolatum Given by Mouth on the Digestion and Absorption of Food".

In the June issue of the American Medical Journal of Surgery, Dr Olsen, in collaboration with Dr James T Case, published an article on "Circumscribed False Peripheral Neuromata".

Dr Wm E Gardner (Fellow), Louisville, Ky, who is Chairman of the Section on Neurology and Psychiatry of the Southern Medical Association, in his an-

nual address to the Section at Asheville, N C, November 12 to 15, will discuss "A Decade of Transition in American Psychiatry"

Dr John F Kenney (Associate), Pawtucket, R I, was recently appointed Consulting Physician to the new Providence Living In Hospital of Providence, Rhode Island, also Associate Physician at St Josephs Hospital of Providence and reappointed Consulting Physician to the Sturdy Memorial Hospital of Attleboro, Mass

Dr H Lisser (Fellow), San Francisco, Calif, is Associate Clinical Professor of Medicine at the University of California Medical School, and Chief of the Ductless Gland Clinic Dr Lisser delivered the Presidential address before the Twelfth Annual Scientific Session of The Association for the Study of Internal Secretions at Minneapolis, June 12, 1928, entitled, "Uni-Glandular Origin of Pluri-Glandular Syndromes, as Illustrated by Disturbances of Menstruation" He is author of the section on "Diseases of the Ductless Glands," Blumer's System of Bedside Diagnosis, published by Saunders and Company, 1928, Third Volume also author, with Dr George Dock (Fellow), Pasadena, chapters on "Diseases of the Ductless Glands," Osler and McCrae "Modern Medicine," Volume 5, 1928 Dr Lisser is also Associate Clinical Editor of "Endocrinology," the official publication of the Association for the Study of Internal Secretions

Dr E Roland Snader, Jr, (Fellow) and Mrs Snader, Philadelphia, are receiving congratulations on the birth of a son, Edward Roland Snader, 3rd, on July 3

Dr and Mrs Carl V Vischer, Philadelphia, and their son Carl V Vischer, 3rd, and daughter Jean Frances Vischer sailed on August 1 on a Canadian cruise to Halifax, Quebec and the Saguenay

Dr Fred C Oldenburg (Fellow), Cleveland, has been promoted to Senior Clinical Instructor in Medicine at Western Reserve Medical College Dr Oldenburg was also

elected Secretary-Treasurer of the Western Reserve Medical Alumni Association

Dr Edward Matzger (Associate), San Francisco, recently received the following appointments Chief of Asthma and Hay Fever Clinic, San Francisco Polyclinic Hospital, Associate in Research, Hooper Foundation, University of California, Consultant Immunologist, Southern Pacific General Hospital, San Francisco, Calif

Dr Matzger is the author of "A Common Sense Viewpoint of the Significance of Skin Tests" and "A Summary to Date of the Technic of Local Passive Transfer," appearing in the May and June numbers, respectively, of California and Western Medicine

Dr Joseph M King (Fellow), Los Angeles, Calif, is a member of the Educational Committee of the new medical school to be opened this fall by the University of Southern California at Los Angeles

Dr James G Carr, Jr (Fellow), Chicago, Ill, has been elected President of the Cook County Hospital Interns' Alumni Association

Dr Ada E Schweitzer (Fellow), Indianapolis, Ind, addressed the Rush County Medical Society on June 12, on health work among school children Dr Schweitzer is Director of Child Hygiene of the Indiana Board of Health

Dr Rutherford B H Gradwohl (Associate), St Louis, Mo, Lt Col, U S Naval Reserve, was on duty with the U S Fleet in Hawaiian waters from April 12 to May 20 of the past spring

Dr Joseph W Larimore (Fellow), St Louis, Mo, has been promoted to Assistant Professor of Medicine at the Washington University Medical School

Dr Estella G Norman (Fellow), Battle Creek, Mich, has been appointed by Governor Fred Green as a member of the Michigan Board of Registration of Nurses and Trained Attendants The law requires that

this Board consist of the State Health Commissioner, one other physician and three registered nurses, the latter usually being superintendents of nurses' training schools

Dr Harold C Bean (Fellow), Portland, Oregon, spoke before the Central Willamette Medical Society on June 7, at Eugene, on the subject "Diagnostic Problems in Internal Medicine"

Dr Walter C Alvarez (Fellow), Rochester, Minn, addressed the Sixth and Eighth Councilor District Medical Societies of Wisconsin, June 11, on "How to Diagnose Gastro-Intestinal Disease from a Good History"

Dr Isidore S Kahn (Fellow), San Antonio, Texas, addressed the Milwaukee, Wisconsin, Oto-Ophthalmic Society, June 8, on "Bronchial Asthma"

Dr Ralph C Matson (Fellow), Portland, Oregon, was elected Vice-President of the American Sanatorium Association at its twenty-third annual meeting in Portland in June

Dr Joseph C Doane (Fellow), Philadelphia, Pa, officiated as President at the annual convention of the American Hospital Association, held in San Francisco, August 6 to 10

Dr Preston M Hickey (Fellow), Ann Arbor, Mich, delivered the Caldwell lecture at the twenty-ninth annual meeting of the American Roentgen Ray Society at Kansas City, Mo, September 25 to 28 Dr Hickey is Professor of Roentgenology at the University of Michigan Medical School

Dr Julian R Blackman (Fellow), of the U S Veterans' Bureau, has received an appointment at Palo Alto, Calif Dr Blackman was formerly Radiologist at the Immanuel Hospital and the U S Veterans' Bureau at Omaha, Nebr

#### OBITUARY

Dr Joseph Bieber, New York, N Y (Fellow, February 24, 1926), died May 16, 1928, of Coronary Embolus and Pulmonary

Infarct, aged 50 Dr Bieber was graduated from the College of Physicians and Surgeons of Columbia University in 1900 and, since 1911, had been attending physician at the People's Hospital He was a member of the Medical Society of the County of New York, the New York State Medical Society and a Fellow of the American Medical Association

#### NEW HOME FOR THE COLLEGE

On October 1, the Executive Offices of The College will be moved from the Covington Hotel in Philadelphia to their permanent new quarters at 133-135 South 36th Street, Philadelphia, which is a newly constructed building used almost exclusively for professional offices The headquarters at the Covington Hotel were purely temporary, awaiting the time when a suitable location could be secured permanently

In the new building there will be ample space for conducting the work and keeping The College records The location faces the campus of the University of Pennsylvania and is in a dignified and educational atmosphere It is readily accessible (only three squares) from the West Philadelphia station of the Pennsylvania Railroad

The headquarters were selected by a sub-committee of The College, and fulfill an urgent need for a permanent College home The Executive Secretary, Mr Loveland, will be especially pleased to have members of The College stop at the headquarters whenever opportunity permits

#### VOLUME FILE FOR ANNALS

The Executive Secretary of The College has had manufactured a suitable volume file for Annals of Internal Medicine This file is in the form of a two section box file, made of durable material and suitable in size to contain one complete volume of Annals It is indexed on the front and may be conveniently placed on the book-shelf where each volume of the Journal may be preserved and where it will be readily accessible for reference The cost, prepaid, is \$1 25

# The Progress of Medical Research in the South\*

By DR T Z CASON, *Jacksonville, Florida*

IN THE last decade the status of the internist has improved and his prestige has greatly increased. If we are to continue to improve and broaden our influence in relation to other groups, or if we are to retrogress, thus becoming only a minor part of the medical profession, depends on certain definite factors. The factors which probably have the greatest influence are keenness of observation and the relations which we shall establish with the other departments of the science in which we are working, especially as these factors relate to research.

Already a considerable amount of pure medical research is being done by the non-medical investigator. There is no objection to this. Part of this research is being done in cooperation with, and part under the direction of the medical worker. On the other hand there is a great deal being done by the non-medical research worker without any medical connection. The problems upon which he works are of his own choosing and his methods of solution are of his own selection. Medical research should be done in

well organized hospitals or in medical schools, that it is being done in colleges and universities without either hospital or medical college affiliations is due largely to the indifference of the medical profession to research. Here the sphere of influence of the internist should be broadened, which fact constitutes one excuse for this paper.

The etiology of a disease may be unknown, however the method of control and treatment may be well established. Conversely, the etiology may be known but the method of transmission or a specific treatment may be unknown. In either case they remain problems for research. When, as in the case of Pellagra, the etiology is not established, the method of transmission or control unknown and the treatment by no means settled, it becomes an important problem for the research worker, the internist and the economist.

I have selected four problems to present to you which are primarily, though not necessarily, Southern, the solution of which requires the closer association of the internists and four other groups, namely, the research worker, the surgeon, the economist and the public health authorities. The

\*Read before the American College of Physicians, March 9, 1928, New Orleans, La.



first problem is that of energy metabolism and may concern the non-medical research worker, the second, one of human resistance which bears directly on the first, presents a problem for the internist and surgeon. The third is that of Pellagra, which in my opinion, is one for the internist, the medical research worker and the economist. The fourth is that of Dengue Fever, which should be solved by the internists and the group composing the public health authorities. The fact that there is, in the South, greater need for research and that there is less cooperation is all the more reason for increased stimulus.

In 1925, the Medical Department of Riverside Hospital began to observe that the basal metabolic rate of young people between the ages of fifteen and twenty-five was from twelve to eighteen percent below the accepted normal standards for individuals of this age. However, this work was not done under the exacting conditions acceptable to the research worker. Inquiries were started as to the possible correctness of this observation. In 1926, Tilt, at the Florida State College for Women, began the study of the basal metabolism of normal young women between the ages of sixteen and twenty-one. Her observations showed them to be from ten to fifteen percent below the normal standards of Dubois and Benedict. A Ozorio de Almeida (1, 2), working in Brazil, showed that white subjects in the Tropics averaged twenty-four percent below generally accepted standards in the United States. He further showed that in one year one subject increased his metabolism from

22.7 calories per square meter to 32 calories by living a life of greater activities. Dr Tilt has made observations on several young women who were assisting in the physical education department and were thus leading more active lives than the ordinary college student. She states "Their metabolism approached more nearly the normal standards, averaging about six to eight percent below." She further states "From the data which I have on about twenty to twenty-five subjects, I am of the opinion that the accepted standards of Dubois and Benedict, which have been compiled from data collected on normal subjects living in Northern sections of the country, probably cannot be applied to normal subjects who live in the South. However, we need considerably more data to prove this statement, hence more research needs to be done." Her investigations were done under conditions acceptable to the research worker and are to be published shortly. Corlette (3), working in Sydney, Australia, on the relation of climate, weather and fat covering to metabolism, concludes that "there is evidence tending to show that the basal metabolism of white men acclimated to living in the Tropics is much less than in colder climates." He bases his findings on his own investigations in Sydney where the conditions are very similar to our own and the findings of Lobato and de Almeida, already referred to. He further concludes, however, that "a thick layer of subcutaneous fat may have an effect on lessening metabolism comparable to that of a hot climate." This may account for the fact that

the metabolism in older persons more nearly approaches the normal standards of the North. Hafkeshing and Borgstrom (4) of New Orleans, investigating the subject, believe that the metabolism of individuals living in New Orleans is definitely lower than the standards, being from minus 14% to minus 18%. They state that the minimum value remains approximately stable from day to day but the time at which it falls varies according to the kind and quantity of food eaten. This led to further inquiry as to the protein intake, the blood pressure, as well as the non-protein nitrogen and urea retention in the blood in individuals living in the South as compared with those living in the North. In 1924, Denis and Borgstrom (5) of Tulane University reported the results on the protein metabolism of two hundred and thirty-three medical students over a period of three years. These results indicated that the average protein intake was lower than that observed for a similar group in New England. They suggested that this might be due to the warm climate, as it was noted that the average protein intake was much higher during the cold weather of February and March than during April and July. In 1927, Wang, Hawks and Wood (6) of the Research Laboratory, Michael Reese Hospital, Chicago, reported the results of their work on the influence of high and low protein diets on blood chemistry. Their work seemed to show that high protein diet produced a marked rise in both total non-protein nitrogen and urea nitrogen but that the values attained in a low protein

diet were within normal range. Their concluding sentence is "attention should again be called to the very high non-protein nitrogen values on the high protein diet." The inference, from their work, is that an individual on a high protein diet will show a marked retention of both total non-protein nitrogen and urea nitrogen, while one on a low protein diet will show but little variation from normal standards. This would indicate to me that the causes for low metabolism in the South and for low total non-protein nitrogen and urea nitrogen in the blood are unsettled. From a questionnaire sent to the different medical schools in the South, on the whole, comparatively little data with regard to the observations on metabolism were obtained. All answers indicated that the present standards for the non-protein and urea nitrogen in the blood of normal patients were suitable for the South. A few answers indicated that the metabolism of normal young people was from slightly to fifteen percent below the normal accepted standards. A few indicated that the metabolism was normal, however, a number did not answer the question. The Medical College of Virginia reported 15% minus, Florida State College 10% to 15% minus, University of North Carolina slightly below, while the Department of Bio-Chemistry, School of Medicine, Tulane University, reported that the standards now used were acceptable. Sufficient data were not obtained to verify the observations at Riverside Hospital of a lower blood pressure in certain of these cases where the basal metabolic rate was persistently low.

If, as one might infer from the results obtained thus far in connection with the correct metabolic standards in the South, the rate is lower among young people, then there arises the question of resistance to disease and the comparative operative risk in the South. Until the problems already presented are solved, this must wait. However, the surgeon and internist should make careful observations and both the surgeon and internist doing inter-change work in the North and South should keep this in mind.

The questionnaire on the subject of Pellagra, which is the third problem, was submitted to the Medical Schools and the State Boards of Health of all the Southern states. The first and a direct question was asked: "Do you know of any recent research work on Pellagra that would leave the question of etiology settled?" With but one exception, the answer was an emphatic "No." While the work of Goldberger (7) and his associates must be appreciated and its value recognized, in so far as solving the problem of the etiology of Pellagra, it has not. Harris (8) thinks Goldberger's experiments in Mississippi were not of great value and that food is of no more importance in the treatment of Pellagra than in the handling of tuberculosis or any other such disease. Jelks of Memphis, who has been interested in this disease for a number of years, denies emphatically that the work of Goldberger has proven anything with reference to the etiology of this disease. Both Harris and Jelks (9) are of the opinion that it is an infectious disease. It is an interesting observation that very recent-

ly authentic cases have been diagnosed in the native-born as far north as Philadelphia (10). The second question of the questionnaire related to the control of Pellagra which, in my opinion, is largely a problem of Economics, or, with Economics, a Public Health and medical problem. The answers to this question indicated that the control of Pellagra is a combination of the three, although they ranged from 75% a health problem to 100% a problem of Economics in the rural districts. It was generally agreed that the etiology was unknown and the treatment was unknown. Until the etiology is established, no adequate explanation can be made as to why a series of cases improves on any accepted dietary regime, while the next series will have a very high mortality under exactly the same treatment. Furthermore, results showed that in Mississippi, in the flood regions of Louisiana and in Texas, the disease is on the increase over the past few years. In the remainder of the South, it is on the decrease. Except for Texas, the increase can be explained by the recent flood in the Mississippi Valley. It thus becomes evident that considerably more research work must be done on this problem. M. L. Graves (11) of Houston, Texas, in answer to this questionnaire, after stating that it is a 50% question of Economics, further states: "all of them are poor people in poor circumstances." His answer was the only attempt to suggest a solution to the Pellagra problem. He states that "100% Government or other surveys must be done by educated sanitarians and physicians with provisions for

proper food," and that "it is an industrial problem in which treatment is directed by physicians"

The fourth problem to be presented is that of Dengue Fever. So far, from the results of work done up to the present time, the etiology of this disease is not known. It is presumably a filtrable virus, though this has not been proven. The work of Siler, Hall and Hitchens (12) on Dengue Fever in the Philippines indicates that Dengue Fever is transmitted by the mosquito, *Aedes aegypti* Linnaeus. With equal positiveness, they prove that the *Culex* is not responsible. Their work on immunity is highly commendable but by no means conclusive. In Florida for a number of years Dengue Fever has occurred in epidemics. The interval between these epidemics is usually five to seven years, or sometimes longer. Furthermore, there are many authentic instances where one individual has had two or more attacks during the epidemic. Silver et al. have made similar observations. Their explanation for the occurrence of epidemics in the Philippines is that it is due to the rainfall, which in turn affects directly the breeding of the *Aedes aegypti*. The recurrence of the disease in the same individual they attribute to inability of the individual to develop immunity from one attack, while, on the other hand, some individuals will develop a life-long immunity from a single attack. Therefore, this within itself becomes a research problem as a part of the whole problem of Dengue Fever. Because of the very low mortality from the disease itself, too little attention is given to it as a medical

problem. Following the last epidemic in Florida the sequelae assumed considerable proportions. For example the reactivation of previously arrested cases of tuberculosis was similar to that following influenza. The period of recovery was much longer than the severity of the disease would normally warrant. That this is also a serious economic problem is indicated in an unpublished statement made by the Jacksonville City Board of Health, following the last epidemic in Jacksonville, that the cost of drugs and medical fees alone during that epidemic was sufficient to have rid Jacksonville forever from all mosquitoes. In this disease, the control seems possible but it will take the co-ordination of the medical profession and Public Health authorities to bring this about.

#### COMMENT

From evidence at hand it is apparent that research in the South is not being done in proportion to that being done in the North. Further, it is evident that the internist, with but few exceptions, is not seriously interested in the doing of research work. His interest is confined to the end results that will help in the diagnosis or the treatment of his patient. He depends too often and too completely upon the research worker to solve all of his problems. This will undoubtedly result in a narrowing of vision and a dullness of perception on the part of the practicing internist. I can see no necessity for the four years medical training to prepare an individual for medical research, but it does seem to be evident that in every instance medi-

cal research should be co-ordinated and that it can be best done by a person with a medical as well as a practical training. It is suggested that co-ordination of research be carried to the extent that, in diseases bearing any relation to heredity, the biologists become a part of the consulting research corps. The answers to my questionnaire indicated that, except for the research work which is being done at Tulane University in New Orleans, which is of the highest type, there is no outstanding research work being done in the South.\* Duke University is preparing to do considerable research, directed particularly at Southern problems. More or less research is being done in some of the other medical colleges but there are a few, both state and sectarian, where no attempt whatever on the part of the medical college is being made to do research, nor is any attempt being made to inspire the medical student with an inquisitive spirit which would lead him to take up these unsolved problems. In some instances the answers to the questionnaires indicated a lamentable lack of knowledge of both Pellagra and Dengue Fever on the part of those in authority in public health positions. Although the question was not asked, no reply indicated that either the absence of research or the small amount being done was due to finances. From observations made in medical centers in the East and Middle West, this would hardly be a legitimate excuse. The lack of research in so many medical schools,

and the absence of the spirit that engenders it, possibly accounts for the lack on the part of the young doctor coming out of college and hospital possessing the desire to investigate thoroughly those problems difficult of solution. That, with the remuneration offered the successful physician and the poor proportional return to the research worker, possibly accounts for the few medical men undertaking pure research.

#### SUMMARY

- 1 The basal metabolic rate, in the South, for young people between the ages of fifteen and twenty-five is apparently below the accepted normal standards.
- 2 In the South resistance to disease and its significance in surgery may depend on the solution of the problem of metabolism.
- 3 The etiology, the method of transmission and the treatment of Pellagra are unknown.
- 4 The etiology of Dengue Fever is not established and the treatment is unknown. A method of control is known. As a medical problem it is of greater importance than is generally accorded the disease.
- 5 Medical research is being done by non-medical workers without proper medical supervision or co-ordination.
- 6 Medical schools, as a whole, are not inspiring the students with either the spirit or the desire for research.
- 7 There is not enough medical research being done in the South.

\*This survey did not extend further north than Virginia.

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# Blackwater Fever<sup>\*</sup>

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IT IS not my intention, and it is not necessary, to go into a general discussion of blackwater fever, and I have already discussed the general problem of hemoglobinuria elsewhere. I do want to stress the importance of examining the urine chemically for hemoglobin, and microscopically for hemoglobin casts and red blood cells, to be sure to differentiate hemoglobinuria from hematuria—two entirely different conditions. I also want to stress the point that, especially after the patient has vomited a few times, the vomitus in blackwater fever contains bright green flecks and shreds of mucus, and the liquid portion of the vomitus is tinged bright green as the mother of one of the cases put it, "What he vomited was as green as the leaves on the trees."

In the earliest reports of this condition from this part of our country, the term "malarial hematuria" is used as the name of the condition, and as soon as it was recognized that the condition was a hemoglobinuria and not a hematuria, the term "malarial hemoglobinuria" is used as the name of the condition, an indication that the early American observers consid-

ered the condition as associated with and a part of malaria. Though a number of theories have been advanced to explain blackwater fever or hemoglobinuria in persons in the tropics or coming from the tropics, the belief has become more and more generally held that the condition is caused by chronic neglected malaria, especially of the subtertian type. In fact, so strong is the general belief today that malaria is far and away the commonest cause of hemoglobinuria in persons in the tropic or coming from the tropics, that one may say that blackwater fever is a synonym for malarial hemoglobinuria. Subtertian malaria is so commonly the cause of blackwater fever that many observers hold that this is the only type of malaria that causes the condition, though most observers admit that tertian or even quartan malaria could be the cause of the condition. There are reports of cases of blackwater fever in persons with tertian malaria, but too often, as in the recent report of Ciavaldini,<sup>\*</sup> there is no record of examination of the blood. All who have worked with

<sup>\*</sup>CIAVALDINI, J. Un cas d'hémoglobinurie chez une paludienne n'ayant jamais absorbé de quinine. *Arch. l'Inst. Past de Algerie*, 1927, v, 48.

<sup>\*</sup>Read before the American College of Physicians, New Orleans, Clinical week, March 9, 1928.

malaria know the danger of accepting a case of malaria in the tropics as a pure tertian unless there is repeated study of the blood. Failure to recognize this point has caused serious results in the use of a supposedly tertian malaria in a man from the tropics in the treatment of general paresis.

binuria have been carefully observed in the hospitals of the Panama Canal for over twenty years, I want just for a minute to call your attention to the conditions there. Table I, published by the Health Commissioner of the Canal Zone, shows the amount of malaria in the Canal Zone from 1905 to 1927 inclusive, and the figures

TABLE I.—CASES OF MALARIA REPORTED TO THE HEALTH DEPARTMENT AMONG EMPLOYEES OF THE PANAMA CANAL AND THE PANAMA RAILROAD

Calendar year	Average force strength	Cases			Rate per 1,000
		White.	Black	Total	
1905	16,511			8,483	514.0
1906	25,547	5,134	16,659	21,793	820.9
1907	39,238	7,973	8,682	16,655	424.5
1908	43,890	6,352	6,020	12,372	281.9
1909	47,167	4,347	5,822	10,169	215.6
1910	50,802	4,884	4,603	9,487	186.7
1911	48,876	4,175	4,812	8,987	183.9
1912	50,893	2,746	2,877	5,623	110.5
1913	56,654	1,477	2,807	4,284	75.6
1914	44,329	950	2,664	3,614	81.5
1915	34,785	606	1,175	1,781	51.2
1916	33,176	180	367	547	16.5
1917	32,589	127	346	473	14.5
1918	25,520	64	410	474	18.6
1919	24,204	103	649	752	31.1
1920	20,673	85	316	401	19.4
1921	14,389	70	144	214	14.9
1922	10,447	56	120	176	16.9
1923	10,976	57	155	212	19.3
1924	11,625	55	135	190	16.3
1925	12,180	84	246	330	27.1
		177	1119	1196	116.1
1926	12,732	58	121	179	14.1
1927	13,560	38	107	145	10.7

NOTE.—Number of cases from 1905 to 1913, inclusive, are those admitted to hospital only. Those shown in 1914, and since, are all cases, whether or not admitted to hospital.

<sup>1</sup>Excluding Bruja Point, where a gang of workmen (nominally Canal employees) was installing large guns for the Army in 1925. Over half these men acquired malaria in 5 months. Since then the area has been sanitized by the Army and very few cases occurred among these workmen in 1926 and 1927.



are eloquent testimony to the constant improvement in the control of malaria until, in 1927, there was the remarkably low rate of 10.7 per thousand. Table 2, compiled from the annual reports of the hospitals in the Canal Zone, shows the number of cases of malaria and of hemoglobinuria treated in the hospitals of the Panama Canal from 1910 to 1927. The diagnosis "clinical malaria" was discontinued in 1917, and the tabulation is a little different for the years following from what it was before

TABLE 2—MALARIA TREATED IN HOSPITALS OF THE PANAMA CANAL, 1910-1917

	Employees only discharged from Panama Canal hospitals				Deaths of employees only			Total deaths in civilian population (including employees)			
	clin mal	sub tert	tert	hgb- uria	sub- tert	tert	hgb- uria	clin mal	sub- tert	tert	hgb- uria
1910	249	4628	952	47	36	0	6	200	80	0	12
1911	2458	5421	836	86	25	0	15	210	69	1	26
1912	1666	3055	760	26	11	0	5	149	71	4	8
1913	994	2531	603	14	12	0	5	74	75	3	7
1914	908	1658	280	4	3	0	0	34	54	4	2
1915	495	838	221	3	2	0	0	0	53	0	3
1916	—*	—*	—*	—*	2	0	0	0	17	3	0
1917	—@	319	99	0	3	0	0	0	19	0	0

MALARIA TREATED IN HOSPITALS OF THE PANAMA CANAL, 1918-1927

	Employees only discharged from Panama Canal hospitals			Military and Naval cases			Total deaths		
	sub- tert	tert	hgb- uria	sub- tert	tert	hgb- uria	sub- tert	tert	hgb- uria
1918	426	111	1	143	75	0	10	1	0
1919	611	235	2	167	93	0	5	1	0
1920	389	175	0	22	12	0	7	0	1
1921	157	136	2	59	78	0	4	2	1
1922	213	110	0	106	46	0	7	1	0
1923	351	99	1	43	29	0	8	0	0
1924	325	126	0	33	19	0	11	0	1
1925	471	149	2	27	25	0	7	0	1
1926	346	156	1	43	33	0	8	0	0
1927	257	127	2	32	31	1	8	0	0

\*Figures not available from annual reports

@ "Clinical malaria" discontinued as a diagnosis

that time. It is notable that the number of cases of hemoglobinuria decreased as the number of cases of malaria decreased. (The figures for 1905 to 1910 are not included here, as they are set forth in the masterly analysis by Deeks and James, which will be considered a little later.)

Last year I had an opportunity to study blackwater fever, especially in Cuba, and, to avoid any uncertainty as to whether blackwater fever in Cuba is the same as blackwater fever in other parts of the world, I have brought with me a specimen of the urine as it is passed by the cases, and I present some charts showing the course of the condition, with notes on the cases. Chart 1 is that of a typical case of blackwater fever in a 14 year old Cuban girl, in whom the blackwater began not over 10 hours before admission to the hospital (second attack). Chart 2 is that of a typical case of blackwater fever in a 16 year old Cuban boy, in whom the blackwater began 2 hours before admission to the hospital (third attack). The blood of case 1 was negative, of case 2 was positive, for malarial parasites on admission to the hospital. Chart 3 is that of a 12 year old Cuban boy, who died in less than thirty hours after the beginning of blackwater. Chart 4 is that of a fatal case in a 20 year old Cuban mulatto, who had blackwater for three days before entering the hospital. Chart 5 is that of a fatal case in a 49 year old Barbadian, who had blackwater 54 hours before entering the hospital. In the last two cases the blood was negative for malarial parasites on ad-

mission to the hospital and throughout their stay in the hospital.

Charts 6 and 7 are interesting. Chart 6 is that of a 37 year old Cuban man, who had two previous attacks of blackwater fever. His blood was negative for malarial parasites on admission to the hospital, and throughout his stay in the hospital, though subtertian gametocytes (crescents) were found in his blood during the survey three or four days before his admission to the hospital. This man came into the hospital complaining of pain in his back and of scanty urine, and developed blackwater fever in the hospital. He was given quinine on admission to the hospital. Chart 7 is that of a 4 year old Cuban girl whose blood contained subtertian gametocytes on admission to the hospital, and contained numerous rings the next day. Her temperature went up in a couple of days, she was given quinine to control the malaria, and after her temperature had returned to normal she had a mild relapse of her blackwater, without rise in temperature. A few days later she was given small doses of quinine without any disturbance.

My study was along two lines (a) Epidemiological studies, and (b) Laboratory Studies. I propose here to say a few words about the epidemiological studies, the laboratory studies, which are, in the nature of things, somewhat technical, to be reported elsewhere. Believing that malaria is the underlying cause of blackwater fever, and with the mode of transmission of malaria known, a large part of my work was to look at the third side of what I have

called the epidemiological triangle, the susceptibility of the population I propose to discuss this question of susceptibility under three heads I Racial Susceptibility, II, Family Susceptibility, and III, Individual Susceptibility

## I RACIAL SUSCEPTIBILITY

All observers of blackwater fever note a difference in the susceptibility of different races to the condition, and always note that the colored races are less susceptible than the white races. As the conditions are commonly such that the native race is colored, and the foreigners are whites, it is often expressed as a greater resistance on the part of the native race, and is often explained as the 'acquirement of immunity in the native race

The figures for different races are brought out in Deeks' and James' report on blackwater fever in the Panama Canal Zone, for the years 1905 to 1910, and Table 3 is a composite of their figures. The figures for the Americans are so modified by the better living conditions and the rapid turnover in this group that the figures do not express the relative susceptibility of the group. In the European and negro groups, it is certain that the negroes did not live under any better conditions than did the Europeans, yet the malaria rate, and the hemoglobinuria rate, are much lower in the negroes than in the Europeans.

About three-fourths of the cases in Europeans were in Spaniards. Table 4 is a tabulation of the labor brought into the Canal Zone during the years

1905 to 1910. This shows that about three fourths of the Europeans were Spaniards, so there is no evidence of any difference in racial susceptibility among the European races. The tabulation does not enable us to determine anything as to differences in susceptibility among the negroes from different regions.

In Cuba I was able to study malaria and blackwater fever in a white race, native to the country, and to compare this race with the Haitian and Jamaican negroes. Here we have the condition of a large number of Haitian negroes brought into the country during the cane cutting season, and returning to Haiti when the cane cutting is over. They are in the country from about the first of January to some time in May. Malaria is common among these negro laborers, but blackwater fever is very rare. But among the native Cubans, blackwater fever is quite prevalent during the four months of March to June, and a few cases occur at any time during the year.

## II FAMILY SUSCEPTIBILITY

Interesting differences in the prevalence of blackwater fever in different families were observed in Cuba. One family is worth reporting in detail.

### FERIA FAMILY

Sixteen persons. Lived in Tacajo Viejo for years, the past two years in Mejia and Julia.

The grandfather is 70 years old, has lived all his life in Tacajo Viejo, and lives there now. Has had much fever, but no blackwater. His wife and children had much fever, but no blackwater.





TABLE 3

Year	Number of cases of malaria per year discharged from Ancon Hospital						
	Annual average number of employees	Total Number of cases discharged	Number of these cases positive	Malaria rate per thousand, based on total number of malaria cases discharged from Ancon Hospital	Number of deaths per year from malaria	Death rate per thousand per year from malaria	Number of cases of hemoglobinuric fever per thousand per year
A Americans							
1905							3.30
1906	5464				7	1.33	1.9
1907	6706				3	0.44	0.7
1908	6572	1004	262	152.8	4	0.60	0.39
1909	6056	1163	267	192	0	0	0.48
1910 to Sept.		571	169				
B Europeans							
1905							5
1906	2000				?	?	5.5
1907	4000				30	7.5	1.25
1908	5811	3786	2598	651.5	25	4.25	5.88
1908	5606	2658	1770	474.1	14	2.38	11.36
1910 to Sept.		1885	1128				
C Negroes							
1905							0.33
1906	26,500				211	7.8	0.59
1907	28,634				146	5.11	0.28
1908	31,507	3747	2309	118.92	25	0.77	0
1909	35,505	5159	3160	145.3	25	0.70	0.25
1910 to Sept.		2776	2025				

Composite table of malaria and hemoglobinuric fever rates in the Canal Zone, 1905 to 1910, from Deeks' and James' Tables IV, V, and VII

EXHIBIT 4—CONTRACT LABORERS BROUGHT TO THE ISTHMIUS BY THE ISTHMIAN CANAL COMMISSION

Country	1904	1905	1906	1907	1908	1909	1910	Total
Spain			1,181	5,291	1,750			8,222
Cuba			500					500
Italy			909	1,032				1,941
France			19					19
Armenia			14					14
Total Europeans			2,623	7,424	1,750			11,797
Barbados	404	3,095	6,510	3,242	2,592	3,605		19,448
Guadaloupe				2,039				2,039
Martinique		2,733	585	2,224				5,542
Jamaica		47						47
Trinidad			1,079				205	1,284
Curacao			23					23
St Kitts			933					933
Fortune Island			361					361
Total West Indians	404	5,875	9,491	7,505	2,592	3,605	205	29,667
Costa Rica		244						244
Colombia		1,077	416					1,493
Panama		334	10	13				357
Not classified			69					69
Grand total	404	7,530	12,609	14,942	4,342	3,605	205	43,432

The father, 46 years old, was born in Gibara, lived in Tacajo Viejo 39 years, came to Mejia 23 months ago (writing in August, 1927), and came to Julia 8 months ago. Has had much fever, but no blackwater. Has always taken quinine. His brothers and sisters had much fever, but no blackwater. Two nephews (sons of a sister) had blackwater in Tacajo Viejo, in the spring of 1927.

The mother, 42 years old, lived in Tacajo Viejo until 23 months ago. Has had much fever, but no blackwater. Always took quinine. She has three brothers, all of whom had much fever, and all had blackwater in Tacajo Viejo. She has two sisters, both have had much fever, but no blackwater. (The husband of one of her sisters died of blackwater.)

The sons and daughters all have had much malaria.

One daughter (17 yrs old) had blackwater once (Mejia, 1925).

One daughter (16 yrs old) had blackwater twice (1 Tacajo Viejo, 1924, 1 Mejia, 1926).

One daughter (15 yrs old) had blackwater once (Mejia, 1926).

One daughter (11 yrs old) had blackwater twice (1 Tacajo Viejo, 1918, 1 Mejia, 1926).

One son (21 yrs old) had blackwater three times, died in third attack (2 Mejia, 1926, 1 Julia, 1927).

One son (18 yrs old) had blackwater five times (2 Tacajo Viejo, 1922, 1924, 3 Mejia, 1926).

One son (13 yrs old) had blackwater once (Mejia, 1926). Had a relapse.

One son (12 yrs old) had blackwater three times (1 Tacajo Viejo, 1919, 2 Mejia, 1926).

One son (9 yrs old) had blackwater once (Mejia, 1926)

That is, 4 daughters had 6 attacks, and 5 sons had 13 attacks, these 9 children had 19 attacks (not counting relapses), all but one attack in the past 5 years. Five attacks were in Tacajó Viejo, 13 attacks were in Mejia, and one attack was in Julia

Of the remaining children

One daughter (4 yrs old) never had blackwater

One son (21 yrs old) never had blackwater

One son (16 yrs old) never had blackwater. Has had much malaria in Tacajó Viejo, Mejia, and Julia

One son (8 yrs old) never had blackwater

One son (2 yrs old) never had blackwater

The husband, wife, and all children, have lived together and under the same conditions continuously

I studied other families with several attacks in the family

On the other hand, there are families who have lived next door to, or across the street from, some of these blackwater families, and have never had a case of blackwater in the family. The Lopez Family, of eleven persons, has lived for twenty-one years in one of the localities which, until the past year, had very high malaria and blackwater rates, but, though they have had much fever, and take quinine, there has never been a case of blackwater in this family. Several such families were studied

It is realized that one must not draw conclusions regarding family susceptibility, at least until much more work has been done—and none are drawn. Malaria may be a house disease, as indicated by James' studies, and the apparent family susceptibility to blackwater fever may be only an

expression of this tendency of malaria to be a house disease

### III INDIVIDUAL SUSCEPTIBILITY

All observers note that a person who has an attack of blackwater fever is quite likely to have another attack. Thomson tabulates the number of attacks in 83 cases he studied in Rhodesia. In the 38 cases and subjects I studied in Cuba, the number of attacks per person was as follows (relapses not counted as attacks)

One attack	Two attacks	Three attacks	Four attacks	Five attacks
26	6	5	0	1

This tendency for a person who has had one attack to have another attack is quite frequently expressed as one attack predisposing to another attack

Another common observation is that a person is likely to have an attack of blackwater in the first six to twenty-four months of residence in the malarious region, if he develops it at all, and this is quite commonly interpreted as meaning the development of an immunity to malaria after that time, with resulting freedom from blackwater. But there is no evidence of development of immunity in the subjects of blackwater fever, in fact, there is a recognized tendency to have repeated attacks, though, of course, most individuals have only one attack

Blackwater fever is rather common in children in Cuba, but we find individuals having their first attack at all ages. Reference to the table of the Feria Family will show that some of the children had the first attack of blackwater when they were very young, others had the first attack after they



were 16 to 18 years of age, and some of them never have had attacks, though all have lived continuously together, and all have had much fever

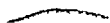
Further study of the individual involves extensive laboratory studies, and, as stated in the beginning, the results of the laboratory studies are being reported elsewhere

The relation of quinine to blackwater fever has merely been touched on in a couple of the case charts, and this phase of the subject has already been discussed elsewhere

#### REMARKS

No conclusions are drawn, and the study is being continued Nothing in

the occurrence of blackwater fever in Cuba is inconsistent with the belief that it is caused by neglected chronic malaria, and everything observed there is in favor of that belief There are striking differences in racial, family, and individual distribution of blackwater in Cuba, but much more information must be collected and studied before conclusions can be drawn Everything observed in Cuba supports the belief that, along with other methods of malaria prophylaxis, the efficient and intelligent use of quinine in the treatment of malaria, and in malaria prophylaxis when required, does not increase the incidence of blackwater fever



# The Dietetic Management of the Diabetic in the Doctor's Office\*

By W H OLMSTED, *St Louis, Missouri*

IT hardly seems necessary to point out that the discovery of insulin has not changed the necessity for measuring the diet of the diabetic individual. Insulin has made diabetic diets more generous in the amount of carbohydrate used. This is most graphically shown by the improvement recorded in diabetic children. With insulin treatment and the resulting increase of carbohydrate intake normal growth and development are usually possible,—quite the opposite picture from the diabetic child of preinsulin days. Today there are two reasons why we must insist that the diabetic measure his food. First, because if insulin and diet are not nicely balanced, either the urine will contain sugar or the patient will experience those very disagreeable reactions accompanying hypoglycemia. Second, definite improvement in tolerance, indicating the increased ability of the patient to produce insulin himself, only follows after years of keeping the urine free of sugar. We have seen no improvement in those cases taking insulin and at the same time constantly showing sugar in the urine. The taking of insulin is no insurance against the

danger of infection when the urine contains sugar.

Granting then that today, as in the past, our diabetics must keep sugar free, it follows that they must measure their food. The physician must assume the role of teacher of dietetics. Through his instruction the diabetic should learn two things. First how to measure the diet, and second, how to estimate its sugar value.

Our present methods of educating the diabetic depend somewhat on whether he is hospitalized or educated by the physician in his office. If the physician decides the case is one he can manage in his office, the patient is usually given a diet list. The carbohydrate food is limited to 5 and 10 per cent vegetables with the addition of a small amount of bread or gluten bread. Little or no effort is made to control the protein or fat.

If the patient is hospitalized, his diabetic education is undertaken by the hospital dietitians, who depend on one of the many excellent manuals for an outline of instruction. The patient is taught to weigh his food. The metric system of weights and measurements is employed. He is taught that he must eat so many grams of the 5 per cent vegetables, so many of 10 per cent, so many grams of meat and butter,

325

\*Read before the American College of Physicians, March 8, 1928, New Orleans, La.



food in terms and quantities long ago forgotten

Because of these difficulties, encountered in the dispensary, hospital and office, we concluded that we needed a rough classification of our diabetics according to their ability to acquire dietetic education. We therefore divided them into three groups. The first group, those seen in the dispensary, who have practically no education and some of them unable to read. These form a group presenting real difficulties. The second group is composed of those with better than third grade public school education, they are usually mild diabetics and are often overweight. This class of patients go to the physician's office. They are not really sick and are unwilling to leave their work for a stay of several weeks in a hospital. They are reluctant to be reeducated into the metric system of measurement and decimal calculations and if forced to weigh their food in grams soon give

up in disgust saying "its all too complicated for a busy person". The third group is divided into three classes the intelligent diabetics, the very severe cases, and the young patients. This group must be taught the decimal and gram system of calculation and measurement. It is not of this group nor the first group that I wish to speak, but of the second.

The modern housewife measures food by cupfuls, tablespoonfuls and teaspoonfuls. The cook books used make use of the standard one-half pint measuring cup, one of these may be found in almost any kitchen. They are marked one-fourth, one-half and three-fourths, one-third and two-thirds. We determined to make this cup our means of measuring food. We took as the unit of carbohydrate measurement a *level* teaspoonful (4 grams). The carbohydrate foods are presented in the manner shown in Table I.

TABLE I  
THE SUGAR VALUE OF FOODS STATED IN HOUSEHOLD MEASUREMENTS

GROUP ONE	
<i>Each Amount of Food Given Below Equals One Teaspoonful of Sugar</i>	
Asparagus .. .. .	$\frac{1}{2}$ cup
Beans, green (canned) .. ..	$\frac{1}{2}$ cup
Cabbage, raw .. ..	$2\frac{1}{4}$ cups
Cabbage, cooked ....	$\frac{3}{8}$ cup
Cauliflower, cooked ..	1 cup
Celery, raw .. .. .	$1\frac{1}{4}$ cups
Celery, cooked .. .. .	$\frac{3}{8}$ cup
Cucumber, sliced .. ..	$\frac{3}{4}$ cup
Egg Plant, cooked .. ..	$\frac{1}{2}$ cup
Endive ....	2 cups
Greens, cooked .. .. .	$\frac{1}{2}$ cup
(Beet, dandelion, mustard, turnip greens)	
Kohlrabi .. .. .	$\frac{1}{2}$ cup
Lettuce, loose .. .. .	2 cups
Lettuce, compact in head .. ..	$\frac{1}{2}$ head
Mushrooms .. .. .	$\frac{1}{2}$ cup
Okra, cooked .. .. .	$\frac{3}{8}$ cup
Pickles, sour .. .. .	$\frac{3}{4}$ cup
Pumpkin, cooked .. .. .	$\frac{1}{2}$ cup
Rhubarb, cooked .. .. .	$\frac{1}{2}$ cup
Sauer Kraut, cooked .. ..	$\frac{3}{8}$ cup
Spinach, cooked .. .. .	$\frac{1}{2}$ cup
Tomatoes, raw .. .. .	$\frac{3}{4}$ cup
Tomatoes, cooked .. .. .	$\frac{1}{2}$ cup
Vegetable Marrow .. .. .	$\frac{1}{2}$ cup
Bran Muffins, Recipe No 2—2 Muffins	
Cocoa, 2 level teaspoonfuls	

## GROUP TWO

*Each Amount of Food Given Below Equals  
Two Teaspoonfuls of Sugar*

Beets, cooked	½ cup	Blackberries	1 cup
Carrots, cooked	½ cup	Cranberries (cooked)	½ cup
Onions, cooked	½ cup	Grapefruit	½ cup
Parsnips, cooked	½ cup	Loganberries	1 cup
Rutabagas, cooked	¾ cup	Strawberries	1 cup
Squash, cooked	½ cup	Watermelon	½ cup
Turnips, cooked	¾ cup	Crackers, Graham, 1 Cracker	

## GROUP THREE

*Each Amount of Food Given Below Equals  
Three Teaspoonfuls of Sugar*

Apple, raw	½ medium	Milk, fresh	1 cup
Apple Sauce	½ cup	Milk, canned	6 tablespoons
Apricots	¾ cup	Corn Flakes	½ cup
Cantaloupe	¼ medium	Crackers, Soda	2 crackers
Cranberries	½ cup	Cream of Wheat—	
Currants, fresh	¾ cup	Dry	2 level tablespoons
Gooseberries	¾ cup	Cooked	½ cup
Lemon Juice	½ cup	Oatmeal, dry	¼ cup
Oranges	½ medium	Oatmeal, cooked	½ cup
Orange Juice	½ cup	Puffed Rice	¾ cup
Pear, fresh	½ medium	Puffed Wheat	1 cup
Peach, fresh	½ medium	Rice, dry	1½ tablespoons
Buttermilk, fresh	1 cup	Rice, cooked	½ cup
Cream, fresh	½ pint		

## GROUP FOUR

*Each Amount of Food Given Below Equals  
Four Teaspoonfuls of Sugar*

Beans, Lima	½ cup	Cherries	¾ cup
Bread (any kind)—		Grapes	¾ cup
½ x 4 x ¾ inches	1 slice	Plums, fresh	1 cup
Peas	½ cup		

## GROUP FIVE

*Five Teaspoonfuls of Sugar*

Banana	½ cup
Bran	½ cup
Corn, canned	½ cup
Pears, canned, no sugar	½ cup
Potato	1 medium

*Nine Teaspoonfuls of Sugar*

Apricots, dried	⅓ cup
Figs	½ cup
Peaches, dried	⅓ cup
Pineapple, canned	⅓ cup
Prunes, dried	¼ cup

The carbohydrate value of each group of foods is stated in teaspoonfuls at the top of each group, the amount of each food equivalent to the stated amount of carbohydrate is presented in fractions of cupfuls after each food. The physician prescribes the amount of carbohydrate to be

taken at each meal as the equivalent of so many teaspoonfuls of sugar. The patient chooses the foods available in such amounts as will make up the number of teaspoonfuls of sugar prescribed. The only education necessary is the ability to add such simple fractions as fourths, halves and thirds.

The unit of measurement for protein is one hundred grams. In order to express this amount in simple language we have chosen the word "serving." One "serving" of such meats as can be measured equals one-half

cupful. In speaking of such meats as are served in cuts, the size is given, thus

*Very thin* (as boiled ham is sliced), size of small plate

*Thin* (about  $\frac{1}{2}$  inch thick), two by five inches

*Thick* (about one inch), two by four inches

The protein foods are divided into two groups. The lean protein foods and fat protein foods.

TABLE 2

GROUP SIX  
THE ALBUMINOUS FOODS

*Lean Meats and Other Foods Which Contain Much More  
Albumin Than Fat*

Beef—Steaks	Lamb—Leg
Cheese, Cottage	Liver
Chicken, Spring	Mutton—Leg
Egg White	Sweetbreads
Fish	Veal
Kidney	

GROUP SEVEN

*Fat Meats and Other Foods Which Contain as Much  
or More Fat Than Albumin*

Beef Tongue	Poultry—Duck, Goose, Fat Chicken,
Cheese—except Cottage	Squab, Turkey
Chops—Lamb or Pork	Roasts—Beef or Pork
Egg Yolk	Sausage
Ham	

GROUP EIGHT

THE FAT FOODS

*Foods Having Much More Fat Than Albumin*

Bacon	Lard
Butter	Oils—Mazola, Olive or Wesson
Cream—Single or Double	

GROUP NINE

*Nuts, Which Have Much Fat, but Also Much Albumin and Sugar*

Almonds	Peanuts (high in sugar)
Brazil Nuts (low in sugar)	Pecans, unpolished
Filberts	Walnuts, California
Hickory Nuts	Walnuts, California soft shell

This arrangement is to facilitate the handling of the overweight diabetic and the one who is not overweight. Meat is the main source of fat for the normal person. In order to reduce a diabetic who is fat we must be sure that he eats lean meats. By this division of meats into a lean and fat group we can control the amount of fat eaten as meat. The protein content of meats does not vary sufficiently in the members of these groups to over-balance the practical value of considering all of the same value. Take, for instance, the commonly used meats of the lean group

	Protein Per Cent	Fat Per Cent
Beef steak, loin	21	20
Chicken	19	16
Salmon, fresh	22	13
Lamb, leg	19	17

Mutton, leg	..	19	18
Veal	...	20	10

And for the fat group

Beef, roast	..	18	25
Cheese, American		29	36
Ham, fresh		16	33
Lamb, chop	..	19	29
Mutton, chop	..	16	33
Pork, chop		16	32

The measurement of protein consists of giving the patient a serving of either group at two of the three meals.

For the unit of fat we have taken a "square" of butter. A square being about one and a quarter inches and one-half inch thick. In the cities we have quarter pound packages of butter for sale. Cut off one-half inch from one of these and one has what we call a "square" of butter. It is ten grams in weight.

TABLE 3

ONE SQUARE OF BUTTER EQUALS—

- ¼ cup of cream,
- 2 tablespoonfuls of double cream,
- ⅔ tablespoonful of mayonnaise,

TWO SQUARES OF BUTTER EQUALS—

- ½ cup of cream,
- ¼ cup of double cream,
- 1½ tablespoonfuls of mayonnaise,
- 1 strip of bacon,
- 2 teaspoonfuls of oil
- 2 muffins,
- 2 strips of bacon,
- 1 tablespoonful of oil,
- 4 muffins

THREE SQUARES OF BUTTER EQUALS—

- ¾ cup of cream,
- ½ cup of double cream,
- 2 tablespoonfuls of olive oil,
- 3 strips of bacon,
- 6 muffins,
- 6 teaspoonfuls of oil

FOUR SQUARES OF BUTTER EQUALS—

- 1 cup of cream,
- ½ cup of double cream,
- 3 tablespoonfuls of mayonnaise,
- 3½ strips of bacon,
- 2 tablespoonfuls of oil

Table 3 shows how the fat foods (Group Eight, Table 2) may be interchanged for the sake of variety. Here is shown that the quarter cup of 16 per cent cream and 10 gram square of butter are interchangeable. The small amount of protein and sugar in cream does not amount to

The physician can increase the protein by increasing the lean protein foods. The fat is increased by using fat meats instead of lean and increasing the butter and cream. Carbohydrate is controlled by increasing or decreasing the number of teaspoonfuls of sugar.

TABLE 4  
MENU  
CALORIES, 2000

*Morning*

Muffins, 2  
Egg, 1  
Bacon, 2 strips

Butter, 1 square  
Cream,  $\frac{1}{4}$  cup  
Fruit, to equal two teaspoonfuls of sugar

*Noon*

Muffins, 2  
Meat, Group Six,  $\frac{1}{2}$  serving  
Cream,  $\frac{1}{2}$  cup

Butter, 2 squares  
Vegetables, Fruit or other food, to equal  
 $4\frac{1}{2}$  teaspoonfuls of sugar

*Night*

Muffins, 2  
Meat, Group Seven, 1 serving  
Cream,  $\frac{1}{2}$  cup

Butter, 2 squares  
Vegetables, Fruit or other food, to equal  
 $4\frac{1}{2}$  teaspoonfuls of sugar

enough to be of importance in the fractional handling of this group of patients.

The physician, in prescribing the diet, specifies the amounts of cream, butter and meat to be taken so that the calories from fat will be supplied.

Table 4 shows the 2000 calorie diet divided into three meals. This table illustrates the method of preparing the stock menu by the aid of which the patient is able to work out his diet from day to day.

Table 5 illustrates five of our maintenance diets quantitatively stated in the practical units of measurement discussed.

Our first statement to the patient when starting the dietetic education is always this: "There is no food you cannot eat providing you measure it. You have a certain number of teaspoonfuls of sugar to spend for each meal, spend the amount for any food you wish." This statement centers the patient's mind on the sugar value of his diet. We insist that he put down in his note book how he has spent his allowance of sugar for each meal. The tables of carbohydrate foods are arranged so as to make this "spending" of sugar easy. The sugar value of each group is a constant amount, while the cup measurement of each food varies.



Our present arrangement of foods by percentage is the reverse of this. The amount of food, namely 100 grams, is constant, while the sugar value of the food varies. If one instructs a patient to take so many hundred grams of 3 per cent vegetables and so many hundred grams of 8 per cent vege-

first try to impress the patient with the fact that he is to have a certain specified amount of sugar, and then show him how to transfer that amount of sugar into cupfuls of food. In this way we have eliminated the "bugbear" of having the patient eat all of the vegetables he wants be-

TABLE 5  
SUMMARY OF MAINTENANCE DIETS  
CUP—TEASPOONFUL

Calories	1800	2000	2200	2400	2600
Lean meat—serving	$\frac{1}{2}$	$\frac{1}{2}$	1	1	1
Fat meat—serving	1	1	1	1	1
Eggs—number	1	1	1	1	1
Bacon—strips	2	2	2	3	3
Butter—squares	5	5	5	7	8½
Cream—cups	$\frac{3}{4}$	1¼	1¼	1¼	1½
Bran Muffins—number	6	6	6	6	6
Sugar—teaspoonfuls	10	11	12	14	14
	Protein	Fat	Carbohydrate		
	Gms	Gms	Gms		
1800 calorie diet	50	150	55		
2000 " "	50	175	65		
2200 " "	60	190	70		
2400 " "	65	220	80		
2600 " "	70	235	80		
Six bran muffins contain	5	30	10		
1 cupful equals 230 c c or grams					
$\frac{1}{2}$ " " 110 " " "					
$\frac{1}{4}$ " " 50 " " "					
$\frac{1}{3}$ " " 75 " " "					

tables, inevitably he gets the erroneous impression that these are the foods he is allowed. He forgets to measure his food because emphasis has been laid on a *Group of Foods* rather than on the *total sugar value* of the food consumed at each meal.

To me success or failure in teaching diabetics depends upon the ability of the dietitian to make the patient think in terms of a quantity of food representing a quantity of sugar. So in presenting carbohydrate foods we

cause, as he says "they are allowed". In calculating each meal, the patient thinks first of the number of teaspoonfuls of sugar he is permitted to have, and then of how to convert that amount of sugar into available food.

The method has other advantages. No occasion can arise where the patient is at a loss what to eat. He can always find carbohydrate food. His problem is simply how much of those foods which are available he can

eat This simplified method makes a splendid introduction to the more exact method of measurement It can be taught to the average housewife in a half hour Then after acquiring experience in the use of the measuring cup she can gradually be taught to weigh with scales by checking the amounts measured with a cup on the scales and finally calculating the content of these amounts of food in grams of carbohydrate

The disadvantage of this scheme is that the measuring cup is at best a crude way of measuring Let me

emphasize again that its use is recommended only for a definite class of patients

My purpose in presenting the results of efforts to educate diabetics is in the hope that you will appreciate the fundamental fact that success is attained only when the dietetic education is adapted to the fundamental education of the patient, his home conditions, his religion, and his willingness to cooperate In our experience success is not attained when one tries to fit a patient to a set method of education

# The Treatment of Diabetes with Special Reference to Accessory Forms of Treatment

By WALTER M BARTLETT, M D, *Bernardsville, New Jersey*

UNDER ordinary circumstances it is simple to determine the specific value of a certain method of treatment of any common disease. The usual procedure is to set aside a group of cases which have been thoroughly investigated, employ the treatment in question in one half of the cases and not in the other half. The results are then compared by some suitable unit of comparison and the statistics resulting are presented to a group of competent judges for inspection and criticism. By this method the comparison is of value only to the extent of the validity and reliability of the unit of comparison. If the unit of comparison is precise and the statistics are significant there can be no question in regard to the conclusion. To prove the value of any therapeutic measure is therefore either simple or impossible. From a statistical standpoint the problem is always the same, from a clinical standpoint it may at times prove more difficult.

Primarily diabetes mellitus is a metabolic disturbance of unique nature. It is in part an intrinsic hereditary endocrine dyscrasia and in part an extrinsic disease due to obesity, char-

acterized by primary failure of the carbohydrate metabolism and secondary anomalous fat and protein combustion. The natural progress of the disease is dependent upon an infinite number of variables. It is a disease whose course is influenced materially, in varying degrees, by heredity, race, weather, diet, digestion, exercise, body weight, temperature, circulation, civilization, age, habitus, and the emotions, as well as being dependent upon the proper function of all other metabolic processes in the human body. It is therefore a task to determine in a broad general manner the influence of one slight factor upon the variable natural course of the disease.

There are certain accepted methods of treating diabetes. The general laws relating to the treatment are agreed upon by the medical profession as a whole. There is considerable disagreement upon insignificant details in the treatment. These disagreements are unavoidable and necessary because it is impossible to prove the value of slight variations in the general treatment of this disease. It is necessary at this time to discuss the use of various accessory forms of treatment in diabetes. It is with the utmost cau-

tion that any positive statements as to the therapeutic value of these accessories will be made

It is essential that the accepted methods employed in the treatment of diabetes be utilized in the fullest sense of the word before any accessory form of treatment can be scientifically utilized or fairly evaluated because of the exacting nature of the pathologic disturbance present. It is therefore essential also that the accepted methods be thoroughly understood before one can utilize or evaluate the accessory in question. To evaluate treatment it is first necessary to understand the course of the disease when untreated. To evaluate an accessory to an accepted treatment it is primarily necessary to understand the course of the disease when modified by the accepted form of treatment. When the individual variations in the natural course of the disease or in the course of the disease when modified by an accepted form of treatment are greatest, the more impossible it becomes to evaluate the accessory. Experience shows that the individual variation in the severity of diabetes is tremendous. Each case is a law unto itself. Likewise the response of the individual case to the general treatment used is quite as variable.

Before discussing the therapeutic value of any substance or method used in the treatment of diabetes it is advisable to enumerate the accepted treatment briefly. The primary importance of dietary regulation has long been recognized. The choice of a diet of the proper and optimum proportions of the three foodstuffs has filled

many volumes of medical literature and has consumed much time in debate and discussion among members of the medical profession. It is quite universally accepted that undernutrition is the fundamental aim of all dietary regulation in the beginning of treatment of diabetes and few will deny that a reduction of the body-weight in obese diabetics is desirable and advantageous.

Second only to diet in importance is the use of insulin. The therapeutic value of insulin, the indications for its employment, and the principles of its application are thoroughly understood. It is universally agreed that no available preparation can at the present time be relied upon to fill the place of insulin in the treatment of diabetes. It is generally accepted that exercise is of value in the treatment of diabetes and particularly vigorous regular daily exercise in the open air and sunlight. Among the subsidiary therapeutic measures employed in the treatment of diabetes it seems advisable to group various factors which have a favorable effect upon the course of the disease. Most important of these is reduction of obesity by low calorie diets. Next in importance is the removal of infectious foci when present. The treatment of infectious processes in the body influences the diabetes favorably. When infections clear up, the diabetes improves, that is, there is a gradual increase in the tolerance for carbohydrate and calories usually noted by a reduction in the insulin requirement.

The improvement of the circulation in cases of cardiac decompensation coincident to diabetes is always favor-

able for improvement of the tolerance. The relief of an existing edema, the proper treatment of a hypertension or the reduction of renal failure with nitrogen retention are all factors which play a rôle in the improvement of a diabetic patient's tolerance for carbohydrate and calories. There are certain preparations on the market at the present time which are alleged to play a part in carbohydrate metabolism and thus have a beneficial effect on diabetic persons. These substances may be of value as an adjunct to the treatments outlined above and will consequently be discussed briefly.

Synthalin or dekyldi-guanidine is claimed to have a beneficial effect on carbohydrate metabolism. It is known to be toxic in doses above 50 mgs per day, after a few days, because of its cumulative effect. The action of synthalin on the blood sugar is mild as compared with insulin and in most cases it sooner or later causes toxic symptoms. The duration of the effect of synthalin is more than 12 hours, so that the toxic symptoms usually arise after the 2nd or 3rd day of administration. These symptoms consist of indigestion, vomiting, headache, fatigue and languor. These symptoms are relieved by vomiting and by the administration of glucose orally or intravenously. Because of the annoying symptoms from synthalin administration it is customary to supplement its use with decholin, an organic preparation derived from bile, which acts as a cholagogue or choleretic, and diminishes the toxicity of synthalin.

Decholin is accordingly always given in doses of 0.5 gm for each 10 mgs

of synthalin. Synthalin can be used in even severe cases of diabetes after considerable experience has been attained. It is not advisable to use it in cases of diabetic coma or in place of insulin in acidosis or in the presence of acute infections. It is not advisable to give more than 30 to 40 mgs of the drug per day in divided doses along with the corresponding doses of decholin. It is always necessary to accomplish the initial desugarization of the diabetic patient by diet or diet and insulin before beginning synthalin therapy. With the use of synthalin there is always a loss of weight and in cases where this is not desirable because of malnutrition or loss of strength the week is sometimes divided into two days of insulin, then two days of synthalin, one day of neither insulin nor synthalin, followed by two more days of synthalin.

The lowering of the blood pressure which occurs under synthalin therapy is interpreted as a toxic sign and, therefore, undesirable. The introduction of intercurrent insulin days prevents loss of weight and abnormal reduction of the blood pressure.

During the past year it was announced in Germany that a new preparation called glukhorment, prepared from fermentation of pancreatic tissue, was efficacious in the treatment of diabetes when administered by mouth. It was soon noted, however, that the physiological effect of this preparation was similar in all respects to that of synthalin. It was then found possible to isolate synthalin from this preparation and it was evident from the nature of the preparation that synthalin had been added.

to the pancreatic fermentation product in its manufacture. For this reason synthalin is preferred as a practical form of treatment and the manufacture of glukhorment has now been discontinued.

In May, 1927, Allen (1) reported the use of blueberry leaf extract in diabetes. The extract was given the name myrtillin (*Myrtomel Squibb*) and it was alleged that this substance played an accessory rôle in carbohydrate metabolism and that it was therefore a useful adjunct in the treatment of diabetes. The basis for these claims consisted of encouraging but inconclusive experiments with depancreatized dogs and indefinite but presumably beneficial results which had been obtained in a few of a large series of diabetic patients. There has been to date no conclusive proof that myrtillin is of value or has any definite or dependable effect upon carbohydrate metabolism. It has been noted that myrtillin is ineffective when administered in the presence of an elevated blood sugar. It is of no value in the presence of infection. It seems to have its most favorable effect when all factors in the treatment tend toward improvement and therefore doubts are justified as to its having any influence on the improvement that is bound to follow. When every other circumstance favors improvement in a given case it seems that myrtillin may increase the spontaneous improvement. This is the most difficult action to determine, because no one can tell just how much of the improvement may have occurred in a particular case without the use of myrtillin. It is commonly

noted that cases improve to a certain extent without myrtillin and sometimes this improvement is quite striking. In many cases there is no effect from the administration of myrtillin, that is, there is no obvious change in the patient's tolerance for carbohydrate or calories. Finally, in differentiating the various degrees of improvement the question is no longer one which can be proven conclusively and one must judge by personal experience over considerable period of observation. It is for this reason that the action of myrtillin in any given case must be described as uncertain and unreliable. In general there seems to be little noticeable difference in a given case whether myrtillin is used or not. In some cases the insulin requirement is reduced by a few units after myrtillin has been started and one becomes encouraged that the diabetes is becoming milder and the patient's tolerance is improving, but it is also true that in many cases where myrtillin is not employed similar improvements or spontaneous variations in insulin requirement occur for either obvious or obscure reasons. Occasionally it is noted that the insulin requirement falls a good deal after myrtillin has been started. This is particularly apt to be true in obese diabetics who have been losing weight rapidly or in cases of abrupt diabetes that are undergoing the process of primary desugarization following which there is always a marked spontaneous return of tolerance.

The first case reported by Allen (Table 1) was an overemphasized initial desugarization improvement associated with undernu-

TABLE 1—USE OF MYRTILLIN IN A CASE NEWLY UNDER TREATMENT\*  
(From Allen 1)

Dates	Diet			Urine		Blood		Insulin, Units	Myrtillin, Gm	Weight Pounds
	Pro- teins	Car- bohy- drate	Calo- ries	Sugar	Ac	Sugar	Time			
1926										
11/21	60	80	1,000	+++	+	242	7 a m	34	—	147
12/ 1	60	80	1,000	++	±	180	7 a m	44	—	147
12/ 5	60	80	1,000	++	0	122	7 a m	46	—	146
12/ 9	60	80	1,000	0	0	139	7 a m	48	—	144
12/14	60	80	1,000	0	+	105	7 a m	48	—	143
12/15	Started myrtillin									
12/18	60	80	1,000	0	0	107	7 a m	40	I	143
12/31	60	80	1,000	0	0	90	1 p m	34		
1927										
1/14	60	80	1,000	0	0	106	1 p m	28	I	144
1/29	60	80	1,000	0	0	111	¾ p m	20	I	141
2/11	60	80	1,000	0	0	107	1 p m	10	I	141
2/25	60	80	1,000	0	0	113	1¼ p m	6	I	139
3/18	60	80	1,200	0	0	93	1 p m	4	I	140
3/25	Stopped insulin									
3/26	60	80	1,200	0	0	112	1 p m	—	I	138
4/ 8	60	80	1,400	0	0	98	1 p m	—	I	140
5/ 9	60	80	1,600	0	0	106	2 p m	—	I	139

TABLE 2—THE EFFECT OF MYRTILLIN IN REDUCING THE INSULIN REQUIREMENT  
(From Allen 1)

Date,	Diet			Urine		Blood		In- sulin, Units	Myrtl- lin, Gm	Weight Pounds
	Pro- tein	Car- bohy- drate	Calo- ries	Sugar	Ac	Sugar	Time			
1924										
8/13	90	100	1,500	++	+	199	7 a m.	30	—	125
8/23	90	100	2,000	—	—	200	7 a m	30	—	125
1925										
6/24	90	100	2,000	0	0	157	7 a.m	34	—	131
7/ 3	90	100	2,000	0	0	125	7 a m	34	—	130
1926										
6/28	90	100	2,200	0	0	150	7 a m	34	—	142
7/ 5	90	100	2,200	0	0	160	7 a m	40	—	142
9/22	90	100	2,200	—	—	Started myrtillin			I	144
9/26	90	100	2,200	0	±	175	7 a m	40	I	144
10/ 1	90	100	2,200	0	±	90	7 a m	35	I	145
10/ 5	90	100	2,200	0	0	55	7 a m	25	I	144+
10/ 9	90	100	2,200	0	0	92	7 a m	10	I	—
10/11	90	100	2,200	0	0	156	7 a m	10	I	—
10/15	90	100	2,200	0	0	200	7 a m	10	I	145
10/17								12	I	—
10/20	90	100	2,200	++	0	146	7 a m	16	I	144
10/25	90	100	2,200	++	0	118	7 a m	16	I	—
10/31	90	100	2,200	0	0	85	7 a m	14	I	144
11/ 5	90	100	2,200	0	0	112	7 a m	14	I	—
1927										
3/ 6	90	100	2,200	0	0	95		14	I	151

trition and consequently is indefinite. The second case (Table 2) reported was that of a youth who was apparently out-growing his diabetes as is commonly seen in any diabetic clinic. By a period of years of accurate dietary control with insulin it is not significant that the insulin was reduced to half the quantity with the introduction of myrtillin. This is not at all definite evidence that myrtillin played any part in the improvement. In the third case (Table 3) proposed as evidence in favor of myrtillin the case was obviously a mild one since the initial blood sugar was only 199 mgs per 100 cc and after a prolonged period of strict dieting it would be possible to control the patient without insulin or myrtillin. The process being speeded up by the introduction of fairly large doses of insulin does not produce any evidence in favor of myrtillin having any important bearing on the improvement which followed. In our entire diabetic experience we find that about sixty to seventy per cent of diabetic patients adhere religiously to strict dietary regulation for a long enough period to improve their tolerance. In the large series of cases of diabetes treated with myrtillin between sixty and seventy per cent of them improved while taking myrtillin to either a small or great extent, as shown by moderate gradual reduction in their insulin requirement. From a biometrical study of a large series of cases it would be impossible to say whether or not myrtillin was responsible for whatever improvement occurred. When a patient is at first given thirty units of insulin per day for some

time and after the introduction of myrtillin gradually is enabled to reduce the insulin dose to half the quantity or none at all, it is not evidence that the myrtillin has acted, but evidence that thirty units of insulin could be given without difficulty in the beginning and could be omitted without difficulty later on, it does not mean that the patient needed the insulin, or, that the myrtillin could take its place in the treatment. From the experience outlined above it is noted that the effect of myrtillin is indefinite and the evidence advanced to show its action is inconclusive. It is therefore not possible to regard myrtillin as a reliable accessory form of treatment in diabetes mellitus.

Scarcely a year passes by that there are not numerous new remedies suggested for the treatment of diabetes. This is true whenever there is difficulty in determining the value of any therapeutic preparation in the treatment of any disease. Diseases which are less thoroughly understood than diabetes and in which there is no specific form of treatment are treated by innumerable methods because it has been found difficult to decide on the evidence at hand which method of treatment is the most beneficial. It is, therefore, no new situation to be unable to prove the value of this new preparation. It seems unfortunate that the clinical experience with the use of this preparation does not offer substantial support to the physiological observations and the animal experiments. This situation is not a new one but nevertheless unfortunate. The general trend of research in diabetic treatment is now directed toward a more conven-



TABLE 3—REDUCTION OF INSULIN DOSAGE THROUGH MYRTILLIN\*  
(From Allen 1)

Date, 1926	Diet			Urine		Blood		In- sulin, Units	Myrtl- lin, Gm	Weight Pounds
	Pro- tein	Car- bohy- drate	Calo- ries			Sugar	Time			
				Sugar	Ac					
3/27	60	60	1,200	+++	++	199	7 a m	40	—	146
						230	1 p m		—	
4/ 5	60	60	1,200	+	++	118	7 a m	46	—	
4/30	80	90	2,000	0	+	156	7 a m	54	—	143
5/ 4	100	100	2,200	0	+	108	7 a m	54	—	144
6/25	100	100	2,200	0	0	125	7 a m	52	—	150
7/16	100	100	2,200	0	0	106	7 a m	50	—	149
7/17	100	100	2,200	0	0	88	7 a m	52	—	
	100	100	2,300					54		
8/	100	100						54	—	
9/								54	—	
10/12			2,300	0	0	186	2 p m	54	—	149
10/15	Started	myrtilin						54	I	
10/26	100	100	2,300	0	0	50	11 a.m	40	I	152†
11/ 5	100	100	2,300	0	0	143	2 p m	36	I	153‡
11/19	100	100	2,300	0	0	88	3 p m	28	I	154
12/ 5	100	100	2,300	0	0	135	2 p m	28	I	154
12/19	100	100	2,300	0	0	104	2 p m	24	I	
12/28	100	100	2,300	0	0	118	3 p m	20	I	154
1927										
1/ 8	100	100	2,300	0	0	114	2 p m	15	I	154
1/22	100	100	2,300	0	0	91	1 p m	10	I	153
2/ 5	100	100	2,300	0	0	121	2 p m	6	I	154
2/18	100	100	2,300	0	0	104	1 3/4 p m	6	I	154
3/11	100	100	2,300	0	0	121	2 p m	6	I	154
3/25	100	100	2,300	0	0	129	2 p m	6	I	155
3/26	100	80	2,300	Stopped insulin				—	I	
4/ 1	100	80	2,300	0	0	115	2 p m	—	I	154
4/ 5	100	80	2,300	0	0	146	1 p m	—	I	155
5/13	100	100	2,300	0	0	106	2 p m	—	I	156

\*The patient was a man, aged 51. Myrtillin enabled him to reduce insulin gradually from 54 units to zero. The diet was not changed except for a brief period from April 1 to May 13, 1927. The body weight increased.

†No symptoms of hypoglycemia.

‡Cold.

ient substitute for insulin that will not have to be taken by hypodermic injection and it is not too early to predict that such will be found.

#### SUMMARY

The difficulty in proving the value of a diabetic remedy has been discussed and the therapeutic requirements of advances in diabetic treat-

ment briefly outlined. The recently alleged accessory forms of treatment have been criticized. The impossibility of determining the therapeutic value of myrtillin has been emphasized.

(1) ALLEN, F. M. Blueberry Leaf Extract, Physiologic and Clinical Properties in Relation to Carbohydrate Metabolism, Journal A. M. A., Nov 5, 1927, lxxxix.

# An Experience with a Ketogenic Dietary in Migraine\*

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THE practice of dietary restriction for the control of hemicranial attacks is well known and doubtless dates back to a time when men or perhaps more often women first experienced such crises. Some migraine victims, long before consulting a physician, have learned to associate their sickness with the ingestion of certain foods and have accordingly omitted them from their dietary often with satisfactory results. The practice has been further extended by physicians who interdict for their patients as nearly as feasibility permits some one of the three great food groups. Even this course has undoubtedly been suggested by patients themselves when they have offered the observation that an increased intake of either carbohydrates, proteins, or fats has been followed by sick headaches and that restriction in one of these three types of food has seemingly been of some benefit. Here and there, either on their own initiative or under direction, individuals have practiced either prolonged or periodic fasting for bilious headaches not without some good effect as it would seem at least to those

who have gone through this experience. Up to the present time various explanations have been offered for the apparent effectivity of either complete or partial dietary restriction in the control of migraine, but many of these explanations are largely theoretical and are open to justifiable adverse criticism.

With a knowledge that diet would seem to have a relationship to the migraine attacks of some individuals it must have occurred to many that the starvation treatment as advocated in epilepsy by Guelpa and Marie (1) abroad and by Geylin in this country must have some reasonable logic in its application. When Wilder (2) in 1921 suggested a high fat diet for the treatment of epilepsy on the hypothesis that the ketone bodies are responsible for the favorable effect of starvation in epilepsy, the conviction of the logic of a ketogenic diet must also have been born home to those who had been observing migraine in relationship to diet. It was only when Peterman (3) in 1925 reported results in the treatment of epilepsy by ketogenic diet that the applicability of this type of diet in migraine suggested itself to me.

There seemed, however, at the time

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very little justification for believing that a ketogenic diet would be of value in the latter disease other than the fact that migraine and epilepsy are disease equivalents, and that what is therapeutically effectual in one might be so in the other. No one had shown that the ketones of themselves bring about the seemingly favorable results of starvation or a high fat diet in epilepsy. Besides this acidosis had and is put down in text book discussions as one of the possible causes of migraine. I have, however, not been able to discover why this is so stated. The probabilities are that this is based on several observations. First—that in the well advanced acidosis of starvation a headache is likely to appear, as far as I know, however, not of the same type that is seen in migraine. Second—that a ketonuria is occasionally a positive finding at some time or other during a migrainal attack, and third—that in some instances (4) it has been observed that a cyclic vomiting child has become a migraine adult and just as earlier in life so in the later attacks, acetone has been found in the urine. The relationship of a ketosis to an explosive attack such as migraine and cyclic vomiting seems to be an uncertain one, perhaps not casual, but rather that it is the result of vomiting and starvation. With this in mind it was easy to theorize that a migraine attack might in some way be terminated by an acidosis, achieved as a result of the starvation and vomiting which the typical hemicranial patient experiences. Wilder's hypothesis made this theory somewhat more attractive. If it were assumed that an acidosis

terminates a migrainal headache then the corollary assumption would attribute the onset of a migrainal attack to an alkalosis.

That this is so has some support in the literature. R and S Weissmann-Netter (5) in 1925 made studies in migrainous attacks occurring in relationship to the menstrual period. A state of decompensated alkalosis was found under such circumstances. This is in marked contrast to their findings of a compensated acidosis just prior to the inauguration of a normal menstrual period. Their studies included estimation of the  $\text{CO}_2$  combining power and the pH of the blood. These authors, however, do not generalize from these findings in applying the conception to all attacks of migraine but feel that some migrainal attacks may have such a basis. In 1924 Forster (6) produced epileptic attacks in epileptics by having such patients practice hyperventilation and in 1926 Muck (7) reported the production of hemicranial attacks in twenty-seven migraine subjects by the same method. Such a circumstance of overbreathing of course brings about a disturbance of the acid base equilibrium due to the excessive loss of carbon dioxide. We have had an opportunity of studying the blood of only one patient in the course of a bilious headache. This patient was not of the ophthalmic variety and showed no change in the  $\text{CO}_2$  combining figures. In two patients during a migraine attack we have found acetone in the urine.

Although the evidence is rather meager to show that migraine attacks are accompanied by a change in the

CHART I DIET CALCULATION TABLE

Fat content of given diet is read directly in grams, protein decided upon and subtracted from C + P column and the remainder is the carbohydrate content of the diet in grams

CALORIES	RATIOS													
	1 I		1 5 I		2 I		2 5 I		3 I		3 5 I		4 I	
	P +		P +		P +		P +		P +		P +		P +	
	F	C	F	C	F	C	F	C	F	C	F	C	F	C
1,000	77	77	86	57	91	45	94	38	97	32	99	28	100	25
	79	79	88	59	93	47	97	39	99	33	101	29	102	26
	81	81	90	60	96	48	99	40	102	34	104	30	105	26
	83	83	92	61	98	49	101	41	104	35	106	30	107	27
1,100	85	85	94	63	100	50	104	41	106	36	108	31	110	27
	87	87	96	64	102	51	106	42	109	36	111	32	112	28
	88	88	99	66	105	52	108	43	111	37	113	32	115	29
	90	90	101	67	107	53	111	44	114	38	116	33	118	29
1,200	92	92	103	69	109	55	113	45	116	39	118	34	120	30
	94	94	105	70	111	56	116	46	118	40	121	34	122	31
	96	96	107	71	114	57	118	47	121	40	123	35	125	31
	98	98	109	73	116	58	120	48	123	41	126	36	127	32
1,300	100	100	111	74	118	59	123	49	126	42	128	37	130	32
	102	102	114	76	120	60	125	50	129	43	130	37	132	33
	104	104	116	77	122	61	128	51	130	43	133	38	135	34
	106	106	119	78	124	62	130	52	132	44	136	39	138	34
1,400	108	108	120	80	128	64	132	53	135	45	138	40	140	35
	110	110	123	82	130	65	135	54	138	46	141	40	142	36
	112	112	125	83	132	66	137	55	141	47	143	41	144	36
	113	113	126	84	134	67	139	56	143	48	146	42	146	37
1,500	115	115	129	86	136	68	141	57	144	48	148	42	150	38
	117	117	131	87	138	69	144	58	147	49	150	43	152	38
	119	119	134	89	140	70	146	59	150	50	152	44	156	39
	121	121	135	90	144	72	150	60	153	51	155	44	158	39
1,600	123	123	137	91	146	73	151	60	156	52	157	45	160	40
	125	125	140	93	149	74	153	61	158	53	161	46	162	41
	127	127	143	94	150	75	155	62	159	53	163	47	165	41
	129	129	144	96	152	76	158	63	162	54	165	47	168	42
1,700	131	131	146	97	154	77	160	64	165	55	168	48	170	43
	133	133	149	99	156	78	163	65	168	56	170	49	172	43
	135	135	150	100	158	79	165	66	170	57	172	49	176	44
	137	137	152	101	162	81	168	67	171	57	175	50	178	44
1,800	138	138	155	103	164	82	170	68	174	58	177	51	180	45
	140	140	156	104	166	83	173	69	177	59	179	51	182	46
	142	142	158	105	168	84	175	70	179	60	182	52	185	46
	144	144	161	107	170	85	178	71	180	60	185	53	188	47
1,900	146	146	162	108	172	86	180	72	183	61	187	54	190	48
	148	148	165	110	176	88	183	73	186	62	189	54	192	48
	150	150	167	111	178	89	185	74	189	63	192	55	195	49
	152	152	168	112	180	90	188	75	192	64	195	56	197	49
2,000	154	154	171	114	182	91	190	76	195	65	197	56	200	50
	156	156	173	116	184	92	191	76	196	65	200	57	202	51
	158	158	176	117	186	93	193	77	198	66	202	58	205	51
	160	160	178	118	189	94	196	78	201	67	204	58	207	52
2,100	162	162	180	120	191	95	198	79	203	68	207	59	210	52
	163	163	182	121	193	97	200	80	206	69	210	60	212	53
	165	165	184	123	196	98	203	81	208	69	212	61	215	54
	167	167	186	124	198	99	205	82	210	70	214	61	217	54
2,200	169	169	189	126	200	100	207	83	213	71	217	62	220	55
	171	171	191	127	202	101	210	84	215	72	220	63	222	56
	173	173	193	128	204	102	212	85	218	73	222	63	225	56
	175	175	195	130	207	103	214	86	220	73	224	64	227	57
2,300	177	177	197	131	209	105	217	87	222	74	227	65	230	57
	179	179	199	133	212	106	219	88	225	75	229	66	232	58
	181	181	202	134	214	107	222	89	228	76	232	66	235	59
	182	182	204	136	216	108	224	90	230	77	234	67	237	59
2,400	185	185	206	137	218	109	226	91	232	77	236	68	240	60
	186	186	208	139	220	110	229	92	235	78	239	68	242	61
	188	188	210	140	222	111	231	93	237	79	242	69	245	61
	190	190	212	141	225	112	233	94	240	80	244	70	247	62
2,500	192	192	214	143	228	114	236	95	242	81	246	70	250	62

From Journal American Dietetic Association, Vol II, No 3, Dec. 1926 Article by Walter M Bartlett, M D

acid base equilibrium, we prescribed a relatively high fat diet in a group of hemispheric patients, and it is the experience with these patients which we wish to tell of at this time. Just as in the diets suggested for epilepsy, so we have in migraine patients kept the carbohydrate intake as low as possible, ranging from 5 to 15 or 20 gms per day. The protein intake has been fixed at about one gm per one

and protein. These patients complained of indigestion with some nausea and vomiting and objected to go on with the diet. On recalculation we discovered the ratio of the diet to be actually 5.2 to 1. Our next two patients were placed on a diet ratio of 2.8 to 1. They, too, complained of indigestion but to a lesser degree. It is noteworthy to say in this connection that although these patients

CHART 2

## MIGRAINE—KETOGENIC DIET

A	{ Patients on Immediate 5 to 1 Ketogenic Diet		3
	{ Patients on Immediate 3 to 1 Ketogenic Diet		2
	Indigestion	5	
	Weekly attacks Relief	1	
	Monthly attacks Relief (3)	0	
	Biyearly attacks Relief (1)	0	
	Acetonuria	5	
	Diabetic Acid	5	
B	Patients Gradually to Ketogenic Diet		18
	No follow up obtained	6	
	Not Relieved	3	
	Acetonuria in Non Reliefs	3	
	(2 to 1 Diet) 2		
	(3 to 1 Diet) 1		
	Relieved	9	
Total Patient's Ketogenic Diet			23

kilogram of body weight and the remainder of the caloric requirement has been supplied by fats. The caloric need for our patients was tentatively estimated on the basis of height, weight, sex and physical activity. Subsequent changes were made dependent upon a loss or gain in weight or upon the complaint of weakness. For the first three patients of this group we unwittingly suggested an immediate change to a diet whose gram ratio value we thought to be according to the (chart 1) plan of Luther and Bartlett, 3 of fat to 1 of carbohydrate

had digestive disturbances, still they had no headaches during the brief period of observation. One of these two patients with weekly attacks, however, remained on the diet long enough to miss to our knowledge two attacks of headache (chart 2). These first five patients deserted us presumably to seek relief elsewhere. At about this time we learned that the shift to a high fat diet should be made gradually and that it is not unusual to have nausea, vomiting, gas, etc., when the change to a ketogenic diet is made abruptly.

CHART 3

*Breakfast*

- 1 Egg
- 1 level teaspoon butter
- 6 crisp strips bacon (cut thin)
- Coffee } with 2 tablespoons heavy cream
- or }
- tea }

*Noon*

- ¼ lb Meat or Chicken
- 2 level tablespoons butter (use 1 tbsp for frying, use 1 t bsp—melt and pour on meat)
- 1 rounded tablespoon of one of the following
- Vegetables—
- Spinach
- Asparagus
- Beet greens
- Dandelions
- Swiss Chard
- String beans (very young)
- Celery (cooked)
- Mushrooms
- Tomatoes
- Brussels Sprouts
- Cauliflower
- Cabbage

- 1 level tablespoon butter
- Lettuce with 1 level tablespoon mayonnaise
- Coffee } with 2 tablespoons heavy cream
- or }
- tea }

*Night*

- 1 Egg
- 6 crisp strips bacon (cut thin)
- 1 rounded tablespoon of one of the vegetables listed above
- 1 level tablespoon butter
- Lettuce with 1 level tablespoon mayonnaise
- Coffee } with 2 tablespoons heavy cream
- or }
- tea }

In the remaining patients we began the regimen with a dietary having a gram ratio of about 1 to 2, increasing the fats and decreasing the carbohydrates every 3 to 4 days. A simple dietary is shown with its caloric

value and gram ratio estimated (chart 4). Of the 18 patients on this plan, 3 patients were not relieved even though a state of ketosis had been established and they seem if anything to have more severe and more frequent attacks. Six other patients did not return frequently enough and

CHART 4

	C/5	P/60	F/185
Eggs—2		12	12
Meat—4 oz		32	20
Bacon 60		10	30
Vegetables, 5%—100	3	2	0
Oil 30 (2T)	0	0	30
Cream (40%) 90	3	3	36
6 T			
Butter 65			55
4 T	6	59	183
1 t			

Total 1929 calories Ratio 2.8 Fat. 1  
Carbohydrate and Protein

were lost even to a follow up. Nine (chart 5) patients had, however, some relief as estimated by frequency of attacks and degree of severity, when attacks were renewed. Three of these patients have had no return of headaches but they happen to have had longer periods of freedom before the inauguration of the diet. Of those whose attacks have recurred, three confessed to a break in diet and an examination of the urine failed to show ketones.

It would seem to be a difficult matter for adults to remain on a ketogenic diet judging from our group of patients. They were ambulatory and not under careful nursing or hospital supervision. It will be seen from our tabulation that the degree of ketosis is no measure of the relief which may be expected in patients

CHART 5—PATIENTS RELIEVED

	Age	Onset	Frequency Recent	Fat Ratio	Aceton- uria	Diacetic Urine	Freedom Time	Subsequent History
1	*28	18	Semi-Weekly	2-1	++	0	3 months	3 attacks in 6 mo
2	32	21	B1-Weekly	3-1	++	+	4 months	2 attacks in 4 mo
3	*21	11	Monthly	2-1	++	+	5 months	Monthly attacks
4	42	16	"	2-1	++	0	3 months	Monthly attacks
5	*36	16	"	1½-1	++	0	6 months	1 attack in 3 mo
6	27	22	"	2-1	+	0	4 months	2 attacks in 4 mo
7	27	14	6 weeks	3-1	++	+	7 months	Free at Present time
8	28	26	B1-Monthly	4-1	+++	++	4 months	Free at Present time
9	39	24	3 months	2-1	++	0	5 months	Free at Present time

taking a high fat diet and that headaches return both with or without a positive ketonuria. All of which leads one to believe that the ketosis of itself just as in epilepsy is not the active factor in achieving relief. Perhaps the ketosis in some way influences some other metabolic function. It is needless to say that for migraine as well as for epilepsy no one has been able to demonstrate a consistent pathological lesion nor an universally acceptable production mechanism. Even the factor of heredity is not as clear as might be. Many etiological theories and therapeutic suggestions have been made for migraine. During the last 20 years at least 8 or 10 methods of treatment have been advanced to our knowledge. It must be evident that it is next to impossible to evaluate therapeutic results in such a disease as migraine—one that often yields at least temporarily when a new doctor is consulted and under his direction a new treatment is carried out. It is a disease that terminates at some time in life permanently or perhaps for a period only to return again. Such remissions to health may occur under many circumstances for no clear reasons. It is likely that

migraine in different individuals has different causes and therefore therapeutic success may come after a varied type of treatment.

Those who are confident that migraine is an allergic manifestation will look upon any success which a ketogenic diet may seem to accomplish as being the result of a chance specific protein withdrawal. Those who are partial to carbohydrate restriction for the treatment of bilious headaches will regard a ketogenic diet as fitting in with their ideas of therapy. Those who regard the liver as the seat of dysfunction will contend that a high fat diet achieves its results by promoting biliary drainage or in some other way influences hepatic function. Those who look to the intestinal tract as the source of mischief in this disease will believe that the ketogenic diet is in keeping with their therapeutic practice and etiological theories. Those who consider duodenal dysfunction as a starting point in the genesis of migraine will also point out that duodenal motility alteration occurs after the ingestion of fat. This method of discussion might be continued with no end and has no purpose here. Obviously we cannot

conclude anything on the strength of our experience. Nine cases out of 23 did show some improvement, however, and we feel sufficiently encouraged to continue with the high fat method. In those with attacks at frequent intervals we will advance the fat content of their diet to the ketogenic point as rapidly as is agreeable to the patient. For those with attacks at longer intervals, we shall suggest a diet at least relatively high in fats and low in carbohydrates, and not too tiresome. For those with attacks coincident with the menstrual period we shall advise such a diet about one week before their expected occurrence. It is hoped that others may have an opportunity to try out a series of patients in a similar way and perhaps study migraine from the acid

base standpoint before, during and after attacks

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# The Influence of Syphilis upon the Course of Other Diseases\*

By JAMES S McLESTER, *Birmingham, Alabama*

THE tendency of Syphilis to produce vague clinical pictures, difficult of recognition, was to the preceding generation of physicians proverbial. Today, however, much of the obscurity which formerly shrouded the manifestations of this disease has been cleared up by the routine use of the Wassermann test, and because of the resulting ease of recognition in its commoner forms, syphilis is no longer looked upon as a potent cause of obscure illness. This change of attitude is not, I submit, entirely justified, as is evidenced, I believe, by clinical experience as well as the well known fact that syphilis, especially in inherited and in old or poorly treated acquired forms, occasionally exists in the presence of a negative or doubtful Wassermann reaction.

Experience inclines me to the belief that the earlier physicians were right in the great respect which they paid to syphilis, for, the more I endeavor to fathom disease complexes which are obscure in their origin or which are difficult to treat, the more do I become impressed with the protean character of late syphilitic manifesta-

tions and with the relative frequency with which this disease is an unsuspected cause of perplexing states of ill health. It is said that a famous surgeon of the post-Civil-War days, as he was nearing the close of a brilliant career, attributed his success largely to the fact that when in doubt he had always prescribed mercury and potassium iodide, to which was added the further reflection that he had not given these drugs often enough.

Volumes have been written upon the symptoms of outspoken syphilis, but comparatively little attention has been given to the relation of so-called latent or unsuspected syphilis to obscure states of ill health or to its influence upon the course of other diseases. Frequently, it is difficult to determine whether syphilis is the sole cause of a poorly defined illness or is merely a complicating factor in the course of some other infection. An example of this was recently seen in the case of a boy of ten years, whose symptoms and roentgenologic signs were typical of simple gastric ulcer, but who was not materially benefitted by the long-continued use of the usual ulcer treatment. His Wassermann reaction and that of his parents was consistently negative, but because of certain suspi-

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cious facts in his mother's history he was finally given mercury and potassium iodide. Immediately his abdominal distress disappeared and he blossomed out like a rose. In a short time he was well and has remained so. Whether this patient had syphilis alone or had a simple peptic ulcer which was prevented from healing by the anemia or other debilitating effect of an inherited syphilis, it is impossible to say. The latter explanation seems to me the more reasonable.

The baneful influence of a complicating syphilitic infection upon the course of pulmonary tuberculosis is well known, but the effect of this complication upon other respiratory infections has received little comment. Illustrative of such influence is the case of a young widow with one healthy child, who has been under my care from time to time during the past five years because of frequent colds which have kept her constantly below par and almost always with a little fever together with utter lack of endurance. Disease of the accessory nasal cavities and a cough which persistently suggested tuberculosis, but which was accompanied by physical and roentgenologic appearances in no wise suggestive of phthisis, recurred constantly. Her Wassermann reaction has always been negative, but finally when I learned that her husband had been treated for syphilis she was given similar treatment. Since this time her troubles have largely disappeared. The cough, anemia, and occasional fever as well as the evidences of sinusitis have subsided, and for the first time in many years she has the strength and sense of well-

being of a normal woman. True, it might be assumed that this patient merely had pulmonary syphilis, which assumption cannot be disproved, but the clinical picture which included a catarrhal type of upper respiratory infection, frequently repeated, as well as mild bronchitis inclined me to the belief that the trouble was not due solely or even primarily to the spirochaete. I am inclined more to attribute her respiratory infections to the bacteria which commonly cause such troubles and to conclude that a hitherto hidden syphilis prevented complete recovery.

Pulmonary syphilis in the form of diffuse gummata or as a general bronchitis has been occasionally observed and requires no comment, but the influence of syphilis upon the course of another specific infection which involves the lung, lobar pneumonia, is less well known. Prior to 1918 when typical lobar pneumonia, rather than the present bronchial type, prevailed in Alabama during the winter months we occasionally saw a patient with lobar pneumonia whose illness pursued the usual course with typical crisis but who, without empyema or other recognizable complication except positive Wassermann Reaction, experienced delayed resolution and a continued post-critical fever. In typical cases after discovery of the existence of syphilis and the administration of appropriate remedies the lung has rapidly cleared up and the fever has promptly subsided. Similar observations have recently been reported by others.

What I have just said of the control sometimes exerted by an under-

lying syphilis over the behavior of other diseases is by way of introduction to the report of a syndrome in which syphilis seems to influence in a characteristic manner the temperature curve of still another specific disease. The patient with typhoid fever who also has untreated syphilis does not in certain instances get well at the expected time. His fever may show a tendency to continue indefinitely. We made this observation first at the Hillman Hospital in Birmingham sixteen years ago, and subsequently have had ample opportunity to confirm its accuracy. It should be said that we have not confused this syndrome with the continued fever sometimes seen in uncomplicated syphilis, for these patients all gave satisfactory bacteriologic or serologic as well as clinical evidence of typhoid fever.

Typical of the group of whom I speak was our first patient, a young white man who entered the hospital with outspoken typhoid fever, and from whose blood the typhoid bacillus was cultivated. He exhibited none of the stigmata of syphilis and, as this was before the Wassermann test had become a routine clinical procedure, syphilis was unsuspected. His illness pursued at first an eventful course and about the end of the fourth week the previously high fever fell by lysis to about  $100^{\circ}$  F, but thereafter with small diurnal fluctuations it remained very near this level. Day after day the fever continued with no tendency toward subsidence and with apparently little effect upon the patient's sense of well being. The man seemed to feel well but gained

little or no weight, and physical examination failed to reveal any complication which could explain the continuance of the fever. At the end of another two weeks the Wassermann reaction was found to be positive, and on the administration of mercury and potassium iodide the fever promptly subsided. The patient then made an uneventful recovery. Since this time four similar cases have appeared, which in all essential features have been so convincingly like this first case as to leave little doubt that a combination of typhoid fever and syphilis may result in a fairly typical temperature cure.

Apparently the syphilis does not at first materially influence the course of the acute illness. The character of the fever, the abdominal symptoms, and the other features are as a rule those ordinarily encountered in typhoid fever. It is only at what may be regarded as the end of the typhoid course that the complication makes itself evident. The fever fails completely to subside. It continues at this relatively low level, promptly to disappear under the influence of syphilitic treatment. We have been unable to observe any other features of this syndrome which are sufficiently characteristic as to warrant comment.

It is recognized, of course, that there are many causes for persistence of the febrile reaction of typhoid fever, but in the group of patients under consideration the association of a positive Wassermann Reaction with the prompt disappearance of the fever on the administration of mercury and iodides, warrants I feel the assumption that a previously unobtrusive

syphilitic infection is in some measure at least responsible for the continued fever

Certain questions suggest themselves. If the spirochaete can be killed in the tissue by high temperature, as is attempted in the malarial treatment of paresis, why doesn't the typhoid fever cure rather than stir up the syphilis? Evidently it does not. What relation, then, have the two diseases to each other? Is this low grade fever which continues day after day to be regarded as evidence primarily of a persistently active typhoid infection, or as the expression of renewed activity in a

previously latent syphilis? Laboratory studies of the patient will not answer this question, for both bacteriologic and serologic evidences of typhoid fever are apt to persist for some time after recovery. Its answer is largely a matter of clinical interpretation. Although the existence of true latency of syphilis in a pathological sense may well be questioned, it seems fair in the syndrome just described to conclude that an asymptomatic syphilis is reawakened by the invasion of typhoid bacilli, and that as the acute bacillary infection subsides the renewed spirochetal activity then makes itself evident in the manner described

# The Treatment of Diabetes with Special Reference to Accessory Forms of Treatment

By WALTER M BARTLETT, M D, *Bernardsville, New Jersey*

UNDER ordinary circumstances it is simple to determine the specific value of a certain method of treatment of any common disease. The usual procedure is to set aside a group of cases which have been thoroughly investigated, employ the treatment in question in one half of the cases and not in the other half. The results are then compared by some suitable unit of comparison and the statistics resulting are presented to a group of competent judges for inspection and criticism. By this method the comparison is of value only to the extent of the validity and reliability of the unit of comparison. If the unit of comparison is precise and the statistics are significant there can be no question in regard to the conclusion. To prove the value of any therapeutic measure is therefore either simple or impossible. From a statistical standpoint the problem is always the same, from a clinical standpoint it may at times prove more difficult.

Primarily diabetes mellitus is a metabolic disturbance of unique nature. It is in part an intrinsic hereditary endocrine dyscrasia and in part an extrinsic disease due to obesity, char-

acterized by primary failure of the carbohydrate metabolism and secondary anomalous fat and protein combustion. The natural progress of the disease is dependent upon an infinite number of variables. It is a disease whose course is influenced materially, in varying degrees, by heredity, race, weather, diet, digestion, exercise, body weight, temperature, circulation, civilization, age, habitus, and the emotions, as well as being dependent upon the proper function of all other metabolic processes in the human body. It is therefore a task to determine in a broad general manner the influence of one slight factor upon the variable natural course of the disease.

There are certain accepted methods of treating diabetes. The general laws relating to the treatment are agreed upon by the medical profession as a whole. There is considerable disagreement upon insignificant details in the treatment. These disagreements are unavoidable and necessary because it is impossible to prove the value of slight variations in the general treatment of this disease. It is necessary at this time to discuss the use of various accessory forms of treatment in diabetes. It is with the utmost cau-

tion that any positive statements as to the therapeutic value of these accessories will be made

It is essential that the accepted methods employed in the treatment of diabetes be utilized in the fullest sense of the word before any accessory form of treatment can be scientifically utilized or fairly evaluated because of the exacting nature of the pathologic disturbance present. It is therefore essential also that the accepted methods be thoroughly understood before one can utilize or evaluate the accessory in question. To evaluate treatment it is first necessary to understand the course of the disease when untreated. To evaluate an accessory to an accepted treatment it is primarily necessary to understand the course of the disease when modified by the accepted form of treatment. When the individual variations in the natural course of the disease or in the course of the disease when modified by an accepted form of treatment are greatest, the more impossible it becomes to evaluate the accessory. Experience shows that the individual variation in the severity of diabetes is tremendous. Each case is a law unto itself. Likewise the response of the individual case to the general treatment used is quite as variable.

Before discussing the therapeutic value of any substance or method used in the treatment of diabetes it is advisable to enumerate the accepted treatment briefly. The primary importance of dietary regulation has long been recognized. The choice of a diet of the proper and optimum proportions of the three foodstuffs has filled

many volumes of medical literature and has consumed much time in debate and discussion among members of the medical profession. It is quite universally accepted that undernutrition is the fundamental aim of all dietary regulation in the beginning of treatment of diabetes and few will deny that a reduction of the body-weight in obese diabetics is desirable and advantageous.

Second only to diet in importance is the use of insulin. The therapeutic value of insulin, the indications for its employment, and the principles of its application are thoroughly understood. It is universally agreed that no available preparation can at the present time be relied upon to fill the place of insulin in the treatment of diabetes. It is generally accepted that exercise is of value in the treatment of diabetes and particularly vigorous regular daily exercise in the open air and sunlight. Among the subsidiary therapeutic measures employed in the treatment of diabetes it seems advisable to group various factors which have a favorable effect upon the course of the disease. Most important of these is reduction of obesity by low calorie diets. Next in importance is the removal of infectious foci when present. The treatment of infectious processes in the body influences the diabetes favorably. When infections clear up, the diabetes improves, that is, there is a gradual increase in the tolerance for carbohydrate and calories usually noted by a reduction in the insulin requirement.

The improvement of the circulation in cases of cardiac decompensation coincident to diabetes is always favor-

able for improvement of the tolerance. The relief of an existing edema, the proper treatment of a hypertension or the reduction of renal failure with nitrogen retention are all factors which play a rôle in the improvement of a diabetic patient's tolerance for carbohydrate and calories. There are certain preparations on the market at the present time which are alleged to play a part in carbohydrate metabolism and thus have a beneficial effect on diabetic persons. These substances may be of value as an adjunct to the treatments outlined above and will consequently be discussed briefly.

Synthalin or dekyldi-guamidine is claimed to have a beneficial effect on carbohydrate metabolism. It is known to be toxic in doses above 50 mgs per day, after a few days, because of its cumulative effect. The action of synthalin on the blood sugar is mild as compared with insulin and in most cases it sooner or later causes toxic symptoms. The duration of the effect of synthalin is more than 12 hours, so that the toxic symptoms usually arise after the 2nd or 3rd day of administration. These symptoms consist of indigestion, vomiting, headache, fatigue and languor. These symptoms are relieved by vomiting and by the administration of glucose orally or intravenously. Because of the annoying symptoms from synthalin administration it is customary to supplement its use with decholin, an organic preparation derived from bile, which acts as a cholagogue or choleretic, and diminishes the toxicity of synthalin.

Decholin is accordingly always given in doses of 0.5 gm for each 10 mgs

of synthalin. Synthalin can be used in even severe cases of diabetes after considerable experience has been attained. It is not advisable to use it in cases of diabetic coma or in place of insulin in acidosis or in the presence of acute infections. It is not advisable to give more than 30 to 40 mgs of the drug per day in divided doses along with the corresponding doses of decholin. It is always necessary to accomplish the initial desugarization of the diabetic patient by diet or diet and insulin before beginning synthalin therapy. With the use of synthalin there is always a loss of weight and in cases where this is not desirable because of malnutrition or loss of strength the week is sometimes divided into two days of insulin, then two days of synthalin, one day of neither insulin nor synthalin, followed by two more days of synthalin.

The lowering of the blood pressure which occurs under synthalin therapy is interpreted as a toxic sign and, therefore, undesirable. The introduction of intercurrent insulin days prevents loss of weight and abnormal reduction of the blood pressure.

During the past year it was announced in Germany that a new preparation called glukhorment, prepared from fermentation of pancreatic tissue, was efficacious in the treatment of diabetes when administered by mouth. It was soon noted, however, that the physiological effect of this preparation was similar in all respects to that of synthalin. It was then found possible to isolate synthalin from this preparation and it was evident from the nature of the preparation that synthalin had been added.

to the pancreatic fermentation product in its manufacture. For this reason synthalin is preferred as a practical form of treatment and the manufacture of glukhorment has now been discontinued.

In May, 1927, Allen (1) reported the use of blueberry leaf extract in diabetes. The extract was given the name myrtillin (*Myrtomel Squibb*) and it was alleged that this substance played an accessory rôle in carbohydrate metabolism and that it was therefore a useful adjunct in the treatment of diabetes. The basis for these claims consisted of encouraging but inconclusive experiments with depancreatized dogs and indefinite but presumably beneficial results which had been obtained in a few of a large series of diabetic patients. There has been to date no conclusive proof that myrtillin is of value or has any definite or dependable effect upon carbohydrate metabolism. It has been noted that myrtillin is ineffective when administered in the presence of an elevated blood sugar. It is of no value in the presence of infection. It seems to have its most favorable effect when all factors in the treatment tend toward improvement and therefore doubts are justified as to its having any influence on the improvement that is bound to follow. When every other circumstance favors improvement in a given case it seems that myrtillin may increase the spontaneous improvement. This is the most difficult action to determine, because no one can tell just how much of the improvement may have occurred in a particular case without the use of myrtillin. It is commonly

noted that cases improve to a certain extent without myrtillin and sometimes this improvement is quite striking. In many cases there is no effect from the administration of myrtillin, that is, there is no obvious change in the patient's tolerance for carbohydrate or calories. Finally, in differentiating the various degrees of improvement the question is no longer one which can be proven conclusively and one must judge by personal experience over considerable period of observation. It is for this reason that the action of myrtillin in any given case must be described as uncertain and unreliable. In general there seems to be little noticeable difference in a given case whether myrtillin is used or not. In some cases the insulin requirement is reduced by a few units after myrtillin has been started and one becomes encouraged that the diabetes is becoming milder and the patient's tolerance is improving, but it is also true that in many cases where myrtillin is not employed similar improvements or spontaneous variations in insulin requirement occur for either obvious or obscure reasons. Occasionally it is noted that the insulin requirement falls a good deal after myrtillin has been started. This is particularly apt to be true in obese diabetics who have been losing weight rapidly or in cases of abrupt diabetes that are undergoing the process of primary desugarization following which there is always a marked spontaneous return of tolerance.

The first case reported by Allen (Table 1) was an overemphasized initial desugarization improvement associated with undernu-



TABLE 1—USE OF MYRTILLIN IN A CASE NEWLY UNDER TREATMENT\*  
(From Allen 1)

Date	Diet			Urine		Blood		Insulin, Units	Myrtillin, Gm	Weight Pounds
	Pro- teins	Car- bohy- drate	Calo- ries	Sugar	Ac	Sugar	Time			
1926										
11/21	60	80	1,000	++++	+	242	7 a m	34	—	147
12/ 1	60	80	1,000	++	±	180	7 a m	44	—	147
12/ 5	60	80	1,000	++	0	122	7 a m	46	—	146
12/ 9	60	80	1,000	0	0	139	7 a m	48	—	144
12/14	60	80	1,000	0	+	105	7 a m	48	—	143
12/15	Started myrtillin									
12/18	60	80	1,000	0	0	107	7 a m	40	1	143
12/31	60	80	1,000	0	0	90	1 p m	34		
1927										
1/14	60	80	1,000	0	0	106	1 p m	28	1	144
1/29	60	80	1,000	0	0	111	¾ p m	20	1	141
2/11	60	80	1,000	0	0	107	1 p m	10	1	141
2/25	60	80	1,000	0	0	113	1¼ p m	6	1	139
3/18	60	80	1,200	0	0	93	1 p m	4	1	140
3/25	Stopped insulin									
3/26	60	80	1,200	0	0	112	1 p m	—	1	138
4/ 8	60	80	1,400	0	0	98	1 p m	—	1	140
5/ 9	60	80	1,600	0	0	106	2 p m	—	1	139

TABLE 2—THE EFFECT OF MYRTILLIN IN REDUCING THE INSULIN REQUIREMENT  
(From Allen 1)

Date,	Diet			Urine		Blood		In- sulin, Units	Myrtil- lin, Gm	Weight Pounds
	Pro- tein	Car- bohy- drate	Calo- ries	Sugar	Ac	Sugar	Time			
1924										
8/13	90	100	1,500	++	+	199	7 a m	30	—	125
8/23	90	100	2,000	—	—	200	7 a m	30	—	125
1925										
6/24	90	100	2,000	0	0	157	7 a.m	34	—	131
7/ 3	90	100	2,000	0	0	125	7 a m	34	—	130
1926										
6/28	90	100	2,200	0	0	150	7 a m	34	—	142
7/ 5	90	100	2,200	0	0	160	7 a m	40	—	142
9/22	90	100	2,200	—	—	Started myrtillin			1	144
9/26	90	100	2,200	0	±	175	7 a m	40	1	144
10/ 1	90	100	2,200	0	±	90	7 a m	35	1	145
10/ 5	90	100	2,200	0	0	55	7 a m	25	1	144+
10/ 9	90	100	2,200	0	0	92	7 a m	10	1	—
10/11	90	100	2,200	0	0	156	7 a m	10	1	—
10/15	90	100	2,200	0	0	200	7 a m	10	1	145
10/17								12	1	—
10/20	90	100	2,200	++	0	146	7 a m	16	1	144
10/25	90	100	2,200	++	0	118	7 a m	16	1	—
10/31	90	100	2,200	0	0	85	7 a m	14	1	144
11/ 5	90	100	2,200	0	0	112	7 a m	14	1	—
1927										
3/ 6	90	100	2,200	0	0	95		14	1	151

trition and consequently is indefinite. The second case (Table 2) reported was that of a youth who was apparently out-growing his diabetes as is commonly seen in any diabetic clinic. By a period of years of accurate dietary control with insulin it is not significant that the insulin was reduced to half the quantity with the introduction of myrtillin. This is not at all definite evidence that myrtillin played any part in the improvement. In the third case (Table 3) proposed as evidence in favor of myrtillin the case was obviously a mild one since the initial blood sugar was only 199 mgs per 100 cc and after a prolonged period of strict dieting it would be possible to control the patient without insulin or myrtillin. The process being speeded up by the introduction of fairly large doses of insulin does not produce any evidence in favor of myrtillin having any important bearing on the improvement which followed. In our entire diabetic experience we find that about sixty to seventy per cent of diabetic patients adhere religiously to strict dietary regulation for a long enough period to improve their tolerance. In the large series of cases of diabetes treated with myrtillin between sixty and seventy per cent of them improved while taking myrtillin to either a small or great extent, as shown by moderate gradual reduction in their insulin requirement. From a biometrical study of a large series of cases it would be impossible to say whether or not myrtillin was responsible for whatever improvement occurred. When a patient is at first given thirty units of insulin per day for some

time and after the introduction of myrtillin gradually is enabled to reduce the insulin dose to half the quantity or none at all, it is not evidence that the myrtillin has acted, but evidence that thirty units of insulin could be given without difficulty in the beginning and could be omitted without difficulty later on, it does not mean that the patient needed the insulin, or, that the myrtillin could take its place in the treatment. From the experience outlined above it is noted that the effect of myrtillin is indefinite and the evidence advanced to show its action is inconclusive. It is therefore not possible to regard myrtillin as a reliable accessory form of treatment in diabetes mellitus.

Scarcely a year passes by that there are not numerous new remedies suggested for the treatment of diabetes. This is true whenever there is difficulty in determining the value of any therapeutic preparation in the treatment of any disease. Diseases which are less thoroughly understood than diabetes and in which there is no specific form of treatment are treated by innumerable methods because it has been found difficult to decide on the evidence at hand which method of treatment is the most beneficial. It is, therefore, no new situation to be unable to prove the value of this new preparation. It seems unfortunate that the clinical experience with the use of this preparation does not offer substantial support to the physiological observations and the animal experiments. This situation is not a new one but nevertheless unfortunate. The general trend of research in diabetic treatment is now directed toward a more conven-

TABLE 3—REDUCTION OF INSULIN DOSAGE THROUGH MYRTILLIN\*  
(From Allen 1)

Date, 1926	Diet			Urine		Blood		In- sulin, Units	Myrtl- lin, Gm	Weight Pounds
	Pro- tein	Car- bohy- drate	Calo- ries	Sugar	Ac	Sugar	Time			
3/27	60	60	1,200	+++	++	199	7 a m	40	—	146
						230	1 p m		—	
4/ 5	60	60	1,200	+	++	118	7 a m	46	—	
4/30	80	90	2,000	0	+	156	7 a m	54	—	143
5/ 4	100	100	2,200	0	+	108	7 a m	54	—	144
6/25	100	100	2,200	0	0	125	7 a m	52	—	150
7/16	100	100	2,200	0	0	106	7 a m	50	—	149
7/17	100	100	2,200	0	0	88	7 a m	52	—	
	100	100	2,300					54		
8/	100	100						54	—	
9/								54	—	
10/12			2,300	0	0	186	2 p m	54	—	149
10/15	Started	myrtillin						54	I	
10/26	100	100	2,300	0	0	50	11 a.m	40	I	152†
11/ 5	100	100	2,300	0	0	143	2 p m	36	I	153‡
11/19	100	100	2,300	0	0	88	3 p m	28	I	154
12/ 5	100	100	2,300	0	0	135	2 p m	28	I	154
12/19	100	100	2,300	0	0	104	2 p m	24	I	
12/28	100	100	2,300	0	0	118	3 p m	20	I	154
1927										
1/ 8	100	100	2,300	0	0	114	2 p m	15	I	154
1/22	100	100	2,300	0	0	91	1 p m	10	I	153
2/ 5	100	100	2,300	0	0	121	2 p m	6	I	154
2/18	100	100	2,300	0	0	104	1 3/4 p m	6	I	154
3/11	100	100	2,300	0	0	121	2 p m	6	I	154
3/25	100	100	2,300	0	0	129	2 p m	6	I	155
3/26	100	80	2,300	Stopped insulin				—	I	
4/ 1	100	80	2,300	0	0	115	2 p m	—	I	154
4/ 5	100	80	2,300	0	0	146	1 p m	—	I	155
5/13	100	100	2,300	0	0	106	2 p m	—	I	156

\*The patient was a man, aged 51. Myrtillin enabled him to reduce insulin gradually from 54 units to zero. The diet was not changed except for a brief period from April 1 to May 13, 1927. The body weight increased.

†No symptoms of hypoglycemia

‡Cold

ient substitute for insulin that will not have to be taken by hypodermic injection and it is not too early to predict that such will be found.

#### SUMMARY

The difficulty in proving the value of a diabetic remedy has been discussed and the therapeutic requirements of advances in diabetic treat-

ment briefly outlined. The recently alleged accessory forms of treatment have been criticized. The impossibility of determining the therapeutic value of myrtillin has been emphasized.

(1) ALLEN, F. M. Blueberry Leaf Extract, Physiologic and Clinical Properties in Relation to Carbohydrate Metabolism, Journal A. M. A., Nov 5, 1927, lxxxix.

# An Experience with a Ketogenic Dietary in Migraine\*

By TRUMAN G. SCHNABEL, M.D., *Philadelphia, Pa.*

THE practice of dietary restriction for the control of hemicranial attacks is well known and doubtless dates back to a time when men or perhaps more often women first experienced such crises. Some migraine victims, long before consulting a physician, have learned to associate their sickness with the ingestion of certain foods and have accordingly omitted them from their dietary often with satisfactory results. The practice has been further extended by physicians who interdict for their patients as nearly as feasibility permits some one of the three great food groups. Even this course has undoubtedly been suggested by patients themselves when they have offered the observation that an increased intake of either carbohydrates, proteins, or fats has been followed by sick headaches and that restriction in one of these three types of food has seemingly been of some benefit. Here and there, either on their own initiative or under direction, individuals have practiced either prolonged or periodic fasting for bilious headaches not without some good effect as it would seem at least to those

who have gone through this experience. Up to the present time various explanations have been offered for the apparent effectivity of either complete or partial dietary restriction in the control of migraine, but many of these explanations are largely theoretical and are open to justifiable adverse criticism.

With a knowledge that diet would seem to have a relationship to the migraine attacks of some individuals it must have occurred to many that the starvation treatment as advocated in epilepsy by Guelpa and Marie (1) abroad and by Geylin in this country must have some reasonable logic in its application. When Wilder (2) in 1921 suggested a high fat diet for the treatment of epilepsy on the hypothesis that the ketone bodies are responsible for the favorable effect of starvation in epilepsy, the conviction of the logic of a ketogenic diet must also have been born home to those who had been observing migraine in relationship to diet. It was only when Peterman (3) in 1925 reported results in the treatment of epilepsy by ketogenic diet that the applicability of this type of diet in migraine suggested itself to me.

There seemed, however, at the time

\*Read before the American College of Physicians, March 8, 1928, New Orleans, La.

very little justification for believing that a ketogenic diet would be of value in the latter disease other than the fact that migraine and epilepsy are disease equivalents, and that what is therapeutically effectual in one might be so in the other. No one had shown that the ketones of themselves bring about the seemingly favorable results of starvation or a high fat diet in epilepsy. Besides this acidosis had and is put down in text book discussions as one of the possible causes of migraine. I have, however, not been able to discover why this is so stated. The probabilities are that this is based on several observations. First—that in the well advanced acidosis of starvation a headache is likely to appear, as far as I know, however, not of the same type that is seen in migraine. Second—that a ketonuria is occasionally a positive finding at some time or other during a migrainal attack, and third—that in some instances (4) it has been observed that a cyclic vomiting child has become a migraine adult and just as earlier in life so in the later attacks, acetone has been found in the urine. The relationship of a ketosis to an explosive attack such as migraine and cyclic vomiting seems to be an uncertain one, perhaps not casual, but rather that it is the result of vomiting and starvation. With this in mind it was easy to theorize that a migraine attack might in some way be terminated by an acidosis, achieved as a result of the starvation and vomiting which the typical hemicranial patient experiences. Wilder's hypothesis made this theory somewhat more attractive. If it were assumed that an acidosis

terminates a migrainal headache then the corollary assumption would attribute the onset of a migrainal attack to an alkalosis.

That this is so has some support in the literature. R and S Weissmann-Netter (5) in 1925 made studies in migrainous attacks occurring in relationship to the menstrual period. A state of decompensated alkalosis was found under such circumstances. This is in marked contrast to their findings of a compensated acidosis just prior to the inauguration of a normal menstrual period. Their studies included estimation of the  $\text{CO}_2$  combining power and the pH of the blood. These authors, however, do not generalize from these findings in applying the conception to all attacks of migraine but feel that some migrainal attacks may have such a basis. In 1924 Forster (6) produced epileptic attacks in epileptics by having such patients practice hyperventilation and in 1926 Muck (7) reported the production of hemicranial attacks in twenty-seven migraine subjects by the same method. Such a circumstance of overbreathing of course brings about a disturbance of the acid base equilibrium due to the excessive loss of carbon dioxide. We have had an opportunity of studying the blood of only one patient in the course of a bilious headache. This patient was not of the ophthalmic variety and showed no change in the  $\text{CO}_2$  combining figures. In two patients during a migraine attack we have found acetone in the urine.

Although the evidence is rather meager to show that migraine attacks are accompanied by a change in the

CHART I DIET CALCULATION TABLE

Fat content of given diet is read directly in grams, protein decided upon and subtracted from C + P column and the remainder is the carbohydrate content of the diet in grams

CALORIES	RATIOS													
	11		151		21		251		31		351		41	
	P		P		P		P		P		P		P	
	F	C	F	C	F	C	F	C	F	C	F	C	F	C
1,000	77	77	86	57	91	45	94	38	97	32	99	28	100	25
	79	79	88	59	93	47	97	39	99	33	101	29	102	26
	81	81	90	60	96	48	99	40	102	34	104	30	105	26
	83	83	92	61	98	49	101	41	104	35	106	30	107	27
1,100	85	85	94	63	100	50	104	41	106	36	108	31	110	27
	87	87	96	64	102	51	106	42	109	36	111	32	112	28
	88	88	99	66	105	52	108	43	111	37	113	32	115	29
	90	90	101	67	107	53	111	44	114	38	116	33	118	29
1,200	92	92	103	69	109	55	113	45	116	39	118	34	120	30
	94	94	105	70	111	56	116	46	118	40	121	34	122	31
	96	96	107	71	114	57	118	47	121	40	123	35	125	31
	98	98	109	73	116	58	120	48	123	41	126	36	127	32
1,300	100	100	111	74	118	59	123	49	126	42	128	37	130	32
	102	102	114	76	120	60	125	50	129	43	130	37	132	33
	104	104	116	77	122	61	128	51	130	43	133	38	135	34
	106	106	119	78	124	62	130	52	132	44	136	39	138	34
1,400	108	108	120	80	128	64	132	53	135	45	138	40	140	35
	110	110	123	82	130	65	135	54	138	46	141	40	142	36
	112	112	125	83	132	66	137	55	141	47	143	41	144	36
	113	113	126	84	134	67	139	56	143	48	146	42	146	37
1,500	115	115	129	86	136	68	141	57	144	48	148	42	150	38
	117	117	131	87	138	69	144	58	147	49	150	43	152	38
	119	119	134	89	140	70	146	59	150	50	152	44	156	39
	121	121	135	90	144	72	150	60	153	51	155	44	158	39
1,600	123	123	137	91	146	73	151	60	156	52	157	45	160	40
	125	125	140	93	149	74	153	61	158	53	161	46	162	41
	127	127	143	94	150	75	155	62	159	53	163	47	165	41
	129	129	144	96	152	76	158	63	162	54	165	47	168	42
1,700	131	131	146	97	154	77	160	64	165	55	168	48	170	43
	133	133	149	99	156	78	163	65	168	56	170	49	172	43
	135	135	150	100	158	79	165	66	170	57	172	49	176	44
	137	137	152	101	162	81	168	67	171	57	175	50	178	44
1,800	138	138	155	103	164	82	170	68	174	58	177	51	180	45
	140	140	156	104	166	83	173	69	177	59	179	51	182	46
	142	142	158	105	168	84	175	70	179	60	182	52	185	46
	144	144	161	107	170	85	178	71	180	60	185	53	188	47
1,900	146	146	162	108	172	86	180	72	183	61	187	54	190	48
	148	148	165	110	176	88	183	73	186	62	189	54	192	48
	150	150	167	111	178	89	185	74	189	63	192	55	195	49
	152	152	168	112	180	90	188	75	192	64	195	56	197	49
2,000	154	154	171	114	182	91	190	76	195	65	197	56	200	50
	156	156	173	116	184	92	191	76	196	65	200	57	202	51
	158	158	176	117	186	93	193	77	198	66	202	58	205	51
	160	160	178	118	189	94	196	78	201	67	204	58	207	52
2,100	162	162	180	120	191	95	198	79	203	68	207	59	210	52
	163	163	182	121	193	97	200	80	206	69	210	60	212	53
	165	165	184	123	196	98	203	81	208	69	212	61	215	54
	167	167	186	124	198	99	205	82	210	70	214	61	217	54
2,200	169	169	189	126	200	100	207	83	213	71	217	62	220	55
	171	171	191	127	202	101	210	84	215	72	220	63	222	56
	173	173	193	128	204	102	212	85	218	73	222	63	225	56
	175	175	195	130	207	103	214	86	220	73	224	64	227	57
2,300	177	177	197	131	209	105	217	87	222	74	227	65	230	57
	179	179	199	133	212	106	219	88	225	75	229	66	232	58
	181	181	202	134	214	107	222	89	228	76	232	66	235	59
	182	182	204	136	216	108	224	90	230	77	234	67	237	59
2,400	185	185	206	137	218	109	226	91	232	77	236	68	240	60
	186	186	208	139	220	110	229	92	235	78	239	68	242	61
	188	188	210	140	222	111	231	93	237	79	242	69	245	61
	190	190	212	141	225	112	233	94	240	80	244	70	247	62
2,500	192	192	214	143	228	114	236	95	242	81	246	70	250	62

acid base equilibrium, we prescribed a relatively high fat diet in a group of hemicranial patients, and it is the experience with these patients which we wish to tell of at this time. Just as in the diets suggested for epilepsy, so we have in migraine patients kept the carbohydrate intake as low as possible, ranging from 5 to 15 or 20 gms per day. The protein intake has been fixed at about one gm per one

and protein. These patients complained of indigestion with some nausea and vomiting and objected to go on with the diet. On recalculation we discovered the ratio of the diet to be actually 5.2 to 1. Our next two patients were placed on a diet ratio of 2.8 to 1. They, too, complained of indigestion but to a lesser degree. It is noteworthy to say in this connection that although these patients

## CHART 2

## MIGRAINE—KETOGENIC DIET

A	{	Patients on Immediate 5 to 1 Ketogenic Diet		3
		Patients on Immediate 3 to 1 Ketogenic Diet		2
		Indigestion	5	
		Weekly attacks Relief	1	
		Monthly attacks Relief (3)	0	
		Biyearly attacks Relief (1)	0	
		Acetonuria	5	
		Diacetic Acid	5	
B		Patients Gradually to Ketogenic Diet		18
		No follow up obtained	6	
		Not Relieved	3	
		Acetonuria in Non Reliefs	3	
		(2 to 1 Diet) 2		
		(3 to 1 Diet) 1		
		Relieved	9	
Total Patient's Ketogenic Diet				23

kilogram of body weight and the remainder of the caloric requirement has been supplied by fats. The caloric need for our patients was tentatively estimated on the basis of height, weight, sex and physical activity. Subsequent changes were made dependent upon a loss or gain in weight or upon the complaint of weakness. For the first three patients of this group we unwittingly suggested an immediate change to a diet whose gram ratio value we thought to be according to the (chart 1) plan of Luther and Partlett 3 of fat to 1 of carbohydrate

had digestive disturbances, still they had no headaches during the brief period of observation. One of these two patients with weekly attacks, however, remained on the diet long enough to miss to our knowledge two attacks of headache (chart 2). These first five patients deserted us presumably to seek relief elsewhere. At about this time we learned that the shift to a high fat diet should be made gradually and that it is not unusual to have nausea, vomiting, gas, etc., when the change to a ketogenic diet is made abruptly.

CHART 3

*Breakfast*

- 1 Egg  
 1 level teaspoon butter  
 6 crisp strips bacon (cut thin)  
 Coffee  
     or } with 2 tablespoons heavy cream  
     tea }

*Noon*

- $\frac{1}{4}$  lb Meat or Chicken  
 2 level tablespoons butter (use 1 tbs for frying, use 1 t bsp—melt and pour on meat)  
 1 rounded tablespoon of one of the following  
 Vegetables—  
     Spinach  
     Asparagus  
     Beet greens  
     Dandelions  
     Swiss Chard  
     String beans  
     (very young)  
 Celery (cooked)  
 Mushrooms  
 Tomatoes  
 Brussels Sprouts  
 Cauliflower  
 Cabbage

- 1 level tablespoon butter  
 Lettuce with 1 level tablespoon mayonnaise  
 Coffee  
     or } with 2 tablespoons heavy cream  
     tea }

*Night*

- 1 Egg  
 6 crisp strips bacon (cut thin)  
 1 rounded tablespoon of one of the vegetables listed above  
 1 level tablespoon butter  
 Lettuce with 1 level tablespoon mayonnaise  
 Coffee  
     or } with 2 tablespoons heavy cream  
     tea }

In the remaining patients we began the regimen with a dietary having a gram ratio of about 1 to 2, increasing the fats and decreasing the carbohydrates every 3 to 4 days. A simple dietary is shown with its caloric

value and gram ratio estimated (chart 4). Of the 18 patients on this plan, 3 patients were not relieved even though a state of ketosis had been established and they seem if anything to have more severe and more frequent attacks. Six other patients did not return frequently enough and

CHART 4

	C/5	P/60	F/185
Eggs—2		12	12
Meat—4 oz		32	20
Bacon 60		10	30
Vegetables, 5%—100	3	2	0
Oil 30 (2T)	0	0	30
Cream (40%) 90	3	3	36
6 T			
Butter 65			55
4 T	6	59	183
1 t			
Total 1929 calories	Ratio 28 Fat. 1		
Carbohydrate and Protein			

were lost even to a follow up. Nine (chart 5) patients had, however, some relief as estimated by frequency of attacks and degree of severity, when attacks were renewed. Three of these patients have had no return of headaches but they happen to have had longer periods of freedom before the inauguration of the diet. Of those whose attacks have recurred, three confessed to a break in diet and an examination of the urine failed to show ketones.

It would seem to be a difficult matter for adults to remain on a ketogenic diet judging from our group of patients. They were ambulatory and not under careful nursing or hospital supervision. It will be seen from our tabulation that the degree of ketosis is no measure of the relief which may be expected in patients



CHART 5—PATIENTS RELIEVED

	Age	Onset	Frequency Recent	Fat Ratio	Aceton- uria	Diacetic Urine	Freedom Time	Subsequent History
1	*28	18	Semi-Weekly	2-1	++	0	3 months	3 attacks in 6 mo
2	32	21	Bi-Weekly	3-1	++	+	4 months	2 attacks in 4 mo
3	*21	11	Monthly	2-1	++	+	5 months	Monthly attacks
4	42	16	"	2-1	++	0	3 months	Monthly attacks
5	*36	16	"	1½-1	++	0	6 months	1 attack in 3 mo
6	27	22	"	2-1	+	0	4 months	2 attacks in 4 mo
7	27	14	6 weeks	3-1	++	+	7 months	Free at Present time
8	28	26	Bi-Monthly	4-1	+++	++	4 months	Free at Present time
9	39	24	3 months	2-1	++	0	5 months	Free at Present time

taking a high fat diet and that headaches return both with or without a positive ketonuria. All of which leads one to believe that the ketosis of itself just as in epilepsy is not the active factor in achieving relief. Perhaps the ketosis in some way influences some other metabolic function. It is needless to say that for migraine as well as for epilepsy no one has been able to demonstrate a consistent pathological lesion nor an universally acceptable production mechanism. Even the factor of heredity is not as clear as might be. Many etiological theories and therapeutic suggestions have been made for migraine. During the last 20 years at least 8 or 10 methods of treatment have been advanced to our knowledge. It must be evident that it is next to impossible to evaluate therapeutic results in such a disease as migraine—one that often yields at least temporarily when a new doctor is consulted and under his direction a new treatment is carried out. It is a disease that terminates at some time in life permanently or perhaps for a period only to return again. Such remissions to health may occur under many circumstances for no clear reasons. It is likely that

migraine in different individuals has different causes and therefore therapeutic success may come after a varied type of treatment.

Those who are confident that migraine is an allergic manifestation will look upon any success which a ketogenic diet may seem to accomplish as being the result of a chance specific protein withdrawal. Those who are partial to carbohydrate restriction for the treatment of bilious headaches will regard a ketogenic diet as fitting in with their ideas of therapy. Those who regard the liver as the seat of dysfunction will contend that a high fat diet achieves its results by promoting biliary drainage or in some other way influences hepatic function. Those who look to the intestinal tract as the source of mischief in this disease will believe that the ketogenic diet is in keeping with their therapeutic practice and etiological theories. Those who consider duodenal dysfunction as a starting point in the genesis of migraine will also point out that duodenal motility alteration occurs after the ingestion of fat. This method of discussion might be continued with no end and has no purpose here. Obviously we cannot

conclude anything on the strength of our experience. Nine cases out of 23 did show some improvement, however, and we feel sufficiently encouraged to continue with the high fat method. In those with attacks at frequent intervals we will advance the fat content of their diet to the ketogenic point as rapidly as is agreeable to the patient. For those with attacks at longer intervals, we shall suggest a diet at least relatively high in fats and low in carbohydrates, and not too tiresome. For those with attacks coincident with the menstrual period we shall advise such a diet about one week before their expected occurrence. It is hoped that others may have an opportunity to try out a series of patients in a similar way and perhaps study migraine from the acid

base standpoint before, during and after attacks

- (1) GUELPA, G, AND MARIA, A Bull gen de therap, 1910, clx 616
- (2) WILDER, R. M Mayo Clinic Bull 1921, 11 307
- (3) PETERMAN, M G J A M A, 1925, lxxxiv 1979
- (4) FAWKES, M Migraine and Acetonuria, Brit M J, 1926, 11 1176
- (5) R. & S WEISSMANN-NETTER Compt rend Soc de biol, 1925, xcii 341-343
- (6) FORSTER Hyperventilation epilepsie, Verbands Deutsche Nervenärzte in Innsbruck, 1924, Leipzig, Verlag Vogel, 1925
- (7) MUCK Hyperventilation Migraine, Münch. Med Wochenschrift, 1926, No 24

# The Influence of Syphilis upon the Course of Other Diseases\*

By JAMES S McLESTER, *Birmingham, Alabama*

THE tendency of Syphilis to produce vague clinical pictures, difficult of recognition, was to the preceding generation of physicians proverbial. Today, however, much of the obscurity which formerly shrouded the manifestations of this disease has been cleared up by the routine use of the Wassermann test, and because of the resulting ease of recognition in its commoner forms, syphilis is no longer looked upon as a potent cause of obscure illness. This change of attitude is not, I submit, entirely justified, as is evidenced, I believe, by clinical experience as well as the well known fact that syphilis, especially in inherited and in old or poorly treated acquired forms, occasionally exists in the presence of a negative or doubtful Wassermann reaction.

Experience inclines me to the belief that the earlier physicians were right in the great respect which they paid to syphilis, for, the more I endeavor to fathom disease complexes which are obscure in their origin or which are difficult to treat, the more do I become impressed with the protean character of late syphilitic manifesta-

tions and with the relative frequency with which this disease is an unsuspected cause of perplexing states of ill health. It is said that a famous surgeon of the post-Civil-War days, as he was nearing the close of a brilliant career, attributed his success largely to the fact that when in doubt he had always prescribed mercury and potassium iodide, to which was added the further reflection that he had not given these drugs often enough.

Volumes have been written upon the symptoms of outspoken syphilis, but comparatively little attention has been given to the relation of so-called latent or unsuspected syphilis to obscure states of ill health or to its influence upon the course of other diseases. Frequently, it is difficult to determine whether syphilis is the sole cause of a poorly defined illness or is merely a complicating factor in the course of some other infection. An example of this was recently seen in the case of a boy of ten years, whose symptoms and roentgenologic signs were typical of simple gastric ulcer, but who was not materially benefitted by the long-continued use of the usual ulcer treatment. His Wassermann reaction and that of his parents was consistently negative, but because of certain suspi-

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cious facts in his mother's history he was finally given mercury and potassium iodide. Immediately his abdominal distress disappeared and he blossomed out like a rose. In a short time he was well and has remained so. Whether this patient had syphilis alone or had a simple peptic ulcer which was prevented from healing by the anemia or other debilitating effect of an inherited syphilis, it is impossible to say. The latter explanation seems to me the more reasonable.

The baneful influence of a complicating syphilitic infection upon the course of pulmonary tuberculosis is well known, but the effect of this complication upon other respiratory infections has received little comment. Illustrative of such influence is the case of a young widow with one healthy child, who has been under my care from time to time during the past five years because of frequent colds which have kept her constantly below par and almost always with a little fever together with utter lack of endurance. Disease of the accessory nasal cavities and a cough which persistently suggested tuberculosis, but which was accompanied by physical and roentgenologic appearances in no wise suggestive of phthisis, recurred constantly. Her Wassermann reaction has always been negative, but finally when I learned that her husband had been treated for syphilis she was given similar treatment. Since this time her troubles have largely disappeared. The cough, anemia, and occasional fever as well as the evidences of sinusitis have subsided, and for the first time in many years she has the strength and sense of well-

being of a normal woman. True, it might be assumed that this patient merely had pulmonary syphilis, which assumption cannot be disproved, but the clinical picture which included a catarrhal type of upper respiratory infection, frequently repeated, as well as mild bronchitis inclined me to the belief that the trouble was not due solely or even primarily to the spirochaete. I am inclined more to attribute her respiratory infections to the bacteria which commonly cause such troubles and to conclude that a hitherto hidden syphilis prevented complete recovery.

Pulmonary syphilis in the form of diffuse gummata or as a general bronchitis has been occasionally observed and requires no comment, but the influence of syphilis upon the course of another specific infection which involves the lung, lobar pneumonia, is less well known. Prior to 1918 when typical lobar pneumonia, rather than the present bronchial type, prevailed in Alabama during the winter months we occasionally saw a patient with lobar pneumonia whose illness pursued the usual course with typical crisis but who, without empyema or other recognizable complication except positive Wassermann Reaction, experienced delayed resolution and a continued post-critical fever. In typical cases after discovery of the existence of syphilis and the administration of appropriate remedies the lung has rapidly cleared up and the fever has promptly subsided. Similar observations have recently been reported by others.

What I have just said of the control sometimes exerted by an under-

lying syphilis over the behavior of other diseases is by way of introduction to the report of a syndrome in which syphilis seems to influence in a characteristic manner the temperature curve of still another specific disease. The patient with typhoid fever who also has untreated syphilis does not in certain instances get well at the expected time. His fever may show a tendency to continue indefinitely. We made this observation first at the Hillman Hospital in Birmingham sixteen years ago, and subsequently have had ample opportunity to confirm its accuracy. It should be said that we have not confused this syndrome with the continued fever sometimes seen in uncomplicated syphilis, for these patients all gave satisfactory bacteriologic or serologic as well as clinical evidence of typhoid fever.

Typical of the group of whom I speak was our first patient, a young white man who entered the hospital with outspoken typhoid fever, and from whose blood the typhoid bacillus was cultivated. He exhibited none of the stigmata of syphilis and, as this was before the Wassermann test had become a routine clinical procedure, syphilis was unsuspected. His illness pursued at first an eventful course and about the end of the fourth week the previously high fever fell by lysis to about  $100^{\circ}$  F, but thereafter with small diurnal fluctuations it remained very near this level. Day after day the fever continued with no tendency toward subsidence and with apparently little effect upon the patient's sense of well being. The man seemed to feel well but gained

little or no weight, and physical examination failed to reveal any complication which could explain the continuance of the fever. At the end of another two weeks the Wassermann reaction was found to be positive, and on the administration of mercury and potassium iodide the fever promptly subsided. The patient then made an uneventful recovery. Since this time four similar cases have appeared, which in all essential features have been so convincingly like this first case as to leave little doubt that a combination of typhoid fever and syphilis may result in a fairly typical temperature curve.

Apparently the syphilis does not at first materially influence the course of the acute illness. The character of the fever, the abdominal symptoms, and the other features are as a rule those ordinarily encountered in typhoid fever. It is only at what may be regarded as the end of the typhoid course that the complication makes itself evident. The fever fails completely to subside. It continues at this relatively low level, promptly to disappear under the influence of syphilitic treatment. We have been unable to observe any other features of this syndrome which are sufficiently characteristic as to warrant comment.

It is recognized, of course, that there are many causes for persistence of the febrile reaction of typhoid fever, but in the group of patients under consideration the association of a positive Wassermann Reaction with the prompt disappearance of the fever on the administration of mercury and iodides, warrants I feel the assumption that a previously unobtrusive

typhilitic infection is in some measure at least responsible for the continued fever

Certain questions suggest themselves. If the spirochaete can be killed in the tissue by high temperature, as is attempted in the malarial treatment of paresis, why doesn't the typhoid fever cure rather than stir up the syphilis? Evidently it does not. What relation, then, have the two diseases to each other? Is this low grade fever which continues day after day to be regarded as evidence primarily of a persistently active typhoid infection, or as the expression of renewed activity in a

previously latent syphilis? Laboratory studies of the patient will not answer this question, for both bacteriologic and serologic evidences of typhoid fever are apt to persist for some time after recovery. Its answer is largely a matter of clinical interpretation. Although the existence of true latency of syphilis in a pathological sense may well be questioned, it seems fair in the syndrome just described to conclude that an asymptomatic syphilis is reawakened by the invasion of typhoid bacilli, and that as the acute bacillary infection subsides the renewed spirochetal activity then makes itself evident in the manner described

# The Practice of Cardiology\*

## A Consideration of the Continuous Care of Heart Patients by the Prolonged Use of Drugs, Physiotherapy and Psychotherapy

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IT IS a privilege indeed to address the American College of Physicians, in the organization of which I took part at the beginning, and to be allowed to speak on a topic which has occupied most of my conscious moments during more than half of my professional life

The idea of the American College of Physicians was discussed by a group of men in New York City shortly after the meeting of the International Medical Congress which was held in London in August, 1913. We had come back to America with vivid recollections of delightful encounters with great men and impressive meetings and ceremonies, but none stand out more vividly than the sermon preached by Dean Inge to the assembled physicians in St Paul's Cathedral. In the opening sentence which still lingers in one's mind he said, "I greet you as defeated captains. You are always doomed to final failure in your encounters with disease." He then went on to draw a beautiful

picture of the character and work of the true physician, struggling with disease, but always doomed to lose his last encounter when death finally claimed each human being, one after another.

This sermon must have particularly impressed those whose life work was the care of cardiac disease.

However, the most casual observer must acknowledge that during the past twenty years a great change has taken place in the treatment of heart disease. This change represents a fundamental alteration in the point of view of the profession towards the science of medicine. But to understand this change we must go back several hundred years and observe the pendulum of medical thought that has first swung one way and then the other.

Early medicine was highly speculative and founded very much upon tradition and superstition as was natural to the more simple, mental processes of the time. Later, men attained a pride in their own intellect and very elaborate, dogmatic theories were erected to explain medical observations and to guide the treatment

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It would be logical to preface this lecture by a review of the knowledge and methods in use before the introduction of graphic methods but time does not permit and the exclusion must not be construed or laid to a lack of appreciation of their vital importance

It is just twenty years since McKenzie completed his great book "Diseases of the Heart" which crystallized the result of his own work and of those who went before. In our enthusiasm for graphic methods we sometimes forget the great service done to cardiology by Gaskell when he formulated the functions of the fibres of the heart muscle. This classification is not by any means perfect or complete, but it is so much better than anything else that it has stood for these many years as a wonderful guide to the understanding of disturbed cardiac function. McKenzie gave due credit to Gaskell for naming the five fundamental functions of the fibres of the heart muscle as stimulus production, excitability, conductivity, contractility and tonicity. McKenzie refined these functions as follows:

"By stimulus production is meant the power which the muscle fibres possess of originating a stimulus which can excite the heart to contract, by excitability is meant the power to receive a stimulus, by contractility is meant the power of conveying a stimulus from fibre to fibre, and by tonicity is meant that function of the heart muscle which keeps the heart during diastole in a state of slight tonic contraction.

The functions of stimulus produc-

tion and excitability are most highly developed at the sinus part of the auricle. The rate of the heart depends upon these functions, an increase of their activity resulting in an increase of the frequency of the cardiac action. The activity of the function of stimulus production varies a good deal, as, for instance, the slight acceleration of the heart during inspiration, and the corresponding slowing which occurs during expiration in the young. When excitability is increased, the heart has also a greater tendency to respond to abnormal or irregular stimuli, hence extrasystoles are more likely to occur. While diminished excitability may lessen the heart rate, it should be remembered that slowing of the ventricular rate may be due to other causes, such as depressed conductivity. When stimulus production and excitability are equal the rhythm of the heart is regular. The pulsus alternans is probably an indication of depressed contractility of the heart. The rate at which the contraction travels from fibre to fibre varies in different parts of the heart. Thus, the impulse spreads in the auricles and ventricles more quickly than it does from auricle to ventricle. In this connection it may be noted that conductivity is observed by estimating the time between the systole of the auricles and ventricles. A lowered state of tonicity results in dilation of the heart and of the auriculo-ventricular orifices.

Immediately after the muscle fibres of the heart have contracted they cannot again be stimulated, in other words, excitability has for the moment disappeared. This is called the

refractory stage Restoration of excitability, however, at once recommences, and steadily increases during diastole When stimulated the cardiac muscle either does not contract at all, or it contracts to the fullest possible extent at the time whether the stimulus be weak or strong There is, therefore, no relation between the strength of the stimulus and the strength of the contraction, it is a case of "all or none"

The longer the time that has elapsed since the previous contraction, the weaker is the stimulus required to bring about further contraction Further, the greater the degree of excitability of the muscle fibres, the weaker is the stimulus required, and the earlier in the refractory period will the heart contract The contractility in the muscle fibres is measured by the degree of contraction The amount of the contraction does not depend upon the strength of the stimulus employed, but varies according to the time at which the stimuli are applied When a contraction occurs early in diastole, the contraction in the succeeding cardiac cycle is weaker than that preceding it Within certain limits the degree of contractility depends upon the length of the preceding diastole, the greater the period of rest, the more perfect and full is the recovery It can, therefore, be readily understood that the greater the heart rate the greater is the possibility of cardiac failure The circulation is carried on most efficiently when the cardiac rate is exactly that which allows the myocardium to recover its full contractility, a rate over or under this being a disadvantage Similar laws

apply to each of the other special functions of the heart muscle In the case of conductivity for example, when conduction occurs, this function has been exercised to the fullest extent possible at the time of stimulation The refractory period follows immediately after the conduction of a stimulus, and during this brief period the muscle fibres cannot again conduct a stimulus, conductivity being completely exhausted Restoration, however, quickly commences, and ultimately the function is restored The extent of the relaxation between the contraction depends upon the degree of tone present, and upon the rate of the heart beat With a slower rate there is, of course, more time for full relaxation"

The management of blood pressure has a large place in the practice of cardiology There is much cardiophilosophy wrapped up in the subject of blood pressure Any man who looks upon blood pressure observations as a matter of pure arithmetic by only attempting to record exactly the systolic and diastolic figures, loses the soul of the whole operation The observation of blood pressure in active practice is one of the nicest procedures in the domain of medicine and is best carried out by use of one of the aneroid instruments After the cuff is applied and the stethoscope is placed over the bend of the elbow the observer studies the effect of various pressures upon the pulsating vessel This observation alone when carried out by one who has done it many thousands of times on many different subjects suffering from different circulatory disorders gives a very

intimate acquaintance with the functional state of the heart and blood vessels. The findings may be recorded as systolic and diastolic pressure but there is a lot more to it. Nothing is more impressive than to apply the cuff to the arm of an individual and hear through the stethoscope the systolic bruit before any pressure is applied. This means a high degree of aortic incompetency and is the first hint of a probable diagnosis of specific disease.

Again, when a very sick person comes under observation and shows no sound in the stethoscope except perhaps between 120 and 140, a very small pulse pressure, one knows immediately that he has to deal with a failing myocardium. The skillful use of the sphygmomanometer is no small part of cardiological observation.

Fluoroscopy is a fast developing art. The old adage "seeing is believing" can be applied to the use of the fluoroscope in cardiology. After observing a great many persons of all sizes and ages suffering from many different cardiac troubles, personal skill in observing and interpreting is acquired and goes very far to remove obscurity in cardiac disease.

Combined fluoroscopic, radiographic and orthodiagraphic examinations of diseased conditions give evidence of the nature of affection through the occurrence of changes in the character of the pulsation, the position of the heart and the size and form of its outline.

In fluoroscopic examinations the lower right border (right auricle) expands extensively during systole in some cases of tricuspid regurgitation.

The upper left border (aorta) gives strong systolic expansions in aortic insufficiency. Whenever the pulsations of the left auricle become visible, as in mitral lesions, they are differentiated by being presystolic in time. Strong pulsations of the pulmonary artery are evident on the left side in cases of persistent ductus arteriosus, or more frequently, when a severe stasis due to mitral lesions is present. Abnormal rhythms, as heart block and pulsus alternans, have been studied and diagnosed by fluoroscopic methods, but this procedure possesses no obvious advantages over auscultation. The asynchronous contraction of the right and left ventricle represented by the notched Q R S of the electrocardiogram was demonstrated by the author at the New York Academy of Medicine, though it must be confessed that all did not agree to the interpretation of the two shadows.

A change may occur in the position of the heart from congenital causes, as situs inversus viscerum, from pleural and pericardial adhesions, or from changes in the intrathoracic volume. These last are very common. Even normal variations are caused by the varying position of the diaphragm. In long-chested individuals the cardiac shadow is long and narrow, the axis being more vertical, while in short-chested individuals or in those in whom the diaphragm is pushed up by abdominal distention, it is broad and assumes a horizontal axis. Its position changes as the diaphragm ascends and descends in respiration. It should be remembered that normally the heart is subject to considerable shifting and undue weight should

not be attached to slight variations in position. If for any pathological cause, such as enlargement of the liver, the right dome of the diaphragm is pushed upward, the heart shadow will be displaced to the left. Pulmonary affections, such as atelectasis, tuberculosis and pneumothorax cause a traction on the heart toward the side of the lesion. On the contrary, pleural effusions, tumors, etc., push the heart toward the opposite side. Any rotation of the heart, of course, modifies the shadow and it is often my custom to have the subject turn completely around behind the fluoroscopic screen.

The heart shadow often decreases whenever the heart accelerates, such as in exercise, tachycardia, after atropine, although the results obtained concerning this point have been discordant. During asthmatic attacks the heart is also reduced in size. A condition simulating this, as far as the effect upon the circulation is concerned, can be produced by the well known experiment of Valsalva which consists in taking a deep inspiration and then, with closed glottis, making a forced expiration. This diminishes the blood content of the heart which accounts for its decreased size.

The heart outline increases after continued hard labor or exercise, pathologically also in nephritis and arteriosclerosis. In these cases an actual hypertrophy resulting from the greater strain to which the heart has continually been subjected is usually the cause. The increase in size (often temporary) associated with acute infections, such as diphtheria, scarlet fever and polyarthritis is no doubt

accounted for by a dilatation of the heart.

The details of the enlargement are of the greatest importance in heart lesions, in which case it is due either to dilatation or to hypertrophy and hence accompanies only lesions of considerable duration and severity. The nature of the dilatation or hypertrophy determines the direction of the enlargement and the contour of the shadow. A left ventricular enlargement takes place to the left. Dilatation or hypertrophy of the right ventricle displaces the shadow partly to the right but also, to a marked degree, upward and to the left. In typical cases of aortic insufficiency the heart shadow is enormously increased toward the left and the contour resembles a horizontal oval or is sometimes called "shoe-shaped." The aortic shadow is increased in width and the apex is never merged with the shadow of the diaphragm. Aortic stenosis causes very similar though less pronounced changes in the radiographic outline. In mitral stenosis the heart shadow which is relatively small, resembles more clearly a vertical oval. The enlarged left auricle becomes prominent on the left margin and above it the pulmonary artery bulges, thus giving the entire left border a step-like appearance. In mitral insufficiency the enlargement tends to be uniform in all directions giving the shadow the appearance of a poorly rounded circle. The right auricular border is distinctly enlarged to the right and the pulmonary artery dilated. The left ventricular shadow is increased toward the left.

For the benefit of those of my audience who are not cardiologists I pause a few moments to give a simple, popular description of the findings of the electrocardiograph and the polygraph, hoping to break the ice and induce others to take up the study

The electrocardiograph has given us methods of recording cardiac function which were undreamed of in the olden days and while a single observation is of vast importance our real satisfaction comes in observing by the electrocardiograph the changes in cardiac function over long periods of time

When a physician is reading a book and meets a line of a foreign language, such as Sanskrit or Hebrew, he can skip it with a clear conscience because he is not expected in his professional capacity to know what it means. But the time is soon coming when any man who skips an electrocardiogram that is used in the description of the heart condition will display a lack of professional knowledge that will be inexcusable. It takes about three months of hard study to grasp the essential points of electrocardiology but the great trouble that comes at the very beginning is that the electrocardiogram does not correspond with the ordinary description of the heart beat as consisting of systole and diastole, nor does it correspond with the sound of the heart as described as the first and second sound

The description of the heart beat as consisting of systole and diastole is entirely inadequate as describing what really takes place, and as regards the sounds of the heart, it is found that auricular contraction does not

make any sound, nor does the ventricular contraction make any sound except at its beginning. So it is much better in attempting to read the electrocardiogram to forget all that has been learned about the heart action and about the heart sounds and the so-called cycles of the heart and to start all over again

In the electrocardiogram we have a record of everything in the nature of muscular activity that takes place in the heart, and the most casual inspection of the electrocardiogram in a healthy person reveals three principal events

Figuratively speaking, from left to right, there is a little mound, a church steeple and a small mountain. In every electrocardiogram this church steeple is always present, though the style of its architecture may vary a good deal. The mountain is also present in all electrocardiograms, but the little hill is absent or displaced a good many times. The little hill represents the contraction of the auricle, the church steeple represents the sharp contraction of the ventricle on its contents, and the mountain represents the squeezing of the contents of the heart into the circulation. So in reading the electrocardiogram the first thing to look for is the church steeple, then walk back a little and look for the hill, then return past the church steeple and inspect the mountain

The little hill is called the P wave. The church steeple, or spike, is called the R wave, and the mountain—representing the work of the ventricle—is called the T wave. The letters P, Q, R, S, T, U were arbitrarily used to name the different waves that

are found in the electrocardiogram. The Q wave is the downward wave following the upward P wave and the S wave is the downward wave following the upward R wave. P, R and T are the principal letters, the others receive scant notice in ordinary clinical work.

I wish somebody would strike a simple method for remembering these things. Perhaps the idea of passing a little hill, then coming to the church at the foot of the mountain will do to remember the waves, but how to fix the letter P as belonging to the hill and the letter R as belonging to the church, and the letter T as belonging to the mountain, I do not know. Perhaps if you try to contrive some way of remembering you will think so much about it that it won't be necessary to have any way to remember it.

After we have learned to recognize the wave of the auricle, and the wave of the ventricular contraction, and the wave of the ventricular work, then we come to the study of the electrocardiogram of a healthy heart. Just as in handwriting, so hearts, in writing their autographs make a great variety of signatures, but the outstanding characteristics in healthy people show the auricle always beating in a regular specified time before the ventricle, and the ventricle taking a specified time to complete its work, and these things recurring regularly without interruption.

There are seven varieties of irregular hearts and a friend of mine the other day did strike a trick for remembering these, which, though rather clumsy, may serve our purpose. He

said, remember the word "ships" and then three A's. Leave out the I in "ships" and we have SHPSAAA.

S stands for sinus arrhythmia, H for heart block, P for premature contractions, S for simple paroxysmal tachycardia, A for auricular flutter, A for auricular fibrillation, A for alternation in the pulse. I have found the "ships" AAA, quite a help when all of a sudden I have to recall this list of irregularities.

In sinus arrhythmia, we find the beats of the heart all right, but the beats do not come at regular intervals, the space between them growing gradually shorter as the pulse is observed over a short period of time.

In heart block we find either a lengthened distance between our little auricular hill and our ventricular church steeple, or we find the distance between the hill and the steeple different in every beat. The former means that the impulse of the heart is delayed between the auricle and the ventricle. The other means that there is no impulse conveyed from the auricle to the ventricle and each beats at its own individual rate.

In premature contractions we have a very peculiar state of affairs that makes a most extraordinary picture. We have a very large church steeple, often turned upside down, and a very large mountain which is also often upside down, but when we come to look for our little mound, it is entirely absent. This means that the ventricle of the heart has undertaken to beat by itself, not waiting to receive its cue from the auricle. The reason that the beat is upside down is that the ventricle started to con-

tract at its apex instead of at its base, thus reversing the electric current

In simple paroxysmal tachycardia we find the beats of the heart very numerous and crowded together, so that very often our auricular mound and our ventricular mountain come together and the hill is lost in the mountain. That means that the auricle started to beat before the ventricle was through beating. At other times the beat is natural enough in its hill, its church steeple and its mountain, but there is no interval between the beats.

Auricular flutter is just what its name implies, that is, a very rapid beating of the auricle like a struggling bird held in your hand. It produces a large number of little mounds that are distributed at regular intervals throughout the electrocardiogram, but at the same time the ventricle is beating and producing its church steeple and its mountain. Sometimes there is a church steeple for every two mounds and sometimes the church steeple and the mounds come irregularly. Often there are three hundred mounds and one hundred and fifty church steeples produced every minute.

In auricular fibrillation our auricular mounds are entirely absent, and are replaced by something that looks like a ploughed field and the church steeple and mountains are present in great numbers but are absolutely irregular in their arrangement. This means that the auricle is trembling and not contracting, being paralyzed.

I have taken the time to give this simple ABC introduction in electro-

cardiology because it seems to me that the great stumbling block in the whole matter is that people do not make a beginning in this study. It is a most fascinating field of work and I am sure will well repay in pleasure and usefulness the effort expended to become familiar with it.

Vital capacity constitutes an additional resource for observing a person subject to heart disease. We have been using it with the last few hundred people but have not yet formulated an independent judgment as to its application. It is a very definite fact, however, that reduced vital capacity is strong evidence of impaired cardiac function and that it varies with the condition of the heart.

In spite of all modern tendencies to the contrary drug treatment still constitutes a most essential element in the practice of cardiology. The development of individual practice is from the complex to the simple. Every physician starts medical life with his mind stored with information as to a vast number of remedies. Twenty five years later he has selected according to his own training and experience a much smaller number of drugs which he applies with infinitely more skill than he did at the beginning.

The tools of the physician are drugs. Paints and brushes are the tools of the artist. Everyone can supply himself with brushes and paint and even if he has selected the proper brush and the proper paint he has not gotten very far towards painting a picture. In the same way the cardiologist when he has selected the proper drug and has decided upon the combinations in which it is to be admin-

istered has not gotten very far towards the curing of the sick person. Everything depends upon the constant adaptation of the remedy, as to time and dose, to the immediate needs of the individual.

Drug treatment might well occupy the whole hour and many more besides but I will limit my consideration of the subject simply to an enumeration of a few drugs that I find especially useful in actual practice. If I neglect to give this subject the time that it merits it is because of its ancient standing which makes emphasis of it unnecessary.

In defense of the limited number and precise form of these drugs I would say that I have always regarded a man's practice as an experimental field in which the office is the laboratory. The more precise and uniform the methods used the more clear are the teachings of experience. No man prescribing many different forms of digitalis for many different people, under different circumstances, can draw nearly so valuable a set of conclusions as when he uses exactly the same preparation as to strength and unit of dosage under all conditions. For that reason I adopted, under the influence of the teaching of the late Professor J. M. Groedel of Bad Nauheim, a half grain tablet of digitalis leaves as the unit of medication and have stuck to it with the result that I have been able to predict, at least in my own practice, about what the reaction will be under various conditions and circumstances.

The choice of this unit was founded upon the fact that three of these tablets in a day, equalling a grain

and a half of digitalis, is the average maintenance dose. I have expounded this to each one of the army of detail men who in course of time have come to me from drug firms and each one has always seemed very much impressed and said he would go back to his firm and have them make up this half grain digitalis tablet. Only within the last few days has my propaganda borne fruit, for I received a circular from Burroughs-Wellcome that they had agreed with my reasoning with regard to half grain units of digitalis and that they would make and dispense the half grain tablet of the leaves. The grain and a half unit of the average proprietary digitalis preparation is entirely too large. It is like a mechanic having nothing in his kit of tools but a great big monkey wrench that would not lend itself to fine adjustment for any really delicate mechanical operation. For these reasons the half grain digitalis tablet is my choice of a unit of medication in digitalis. The too large habitual unit has led to discouragement to many physicians who have tried to learn what I consider the acme of cardiologival achievement, and that is the continuous treatment method for persons subject to attacks of decompensation.

I will mention only five drugs. The next one is quinidine. Here, again, the druggist does not give us a satisfactory tablet, if indeed he gives us any tablet at all. I use a two grain tablet which is of much value as a heart sedative in the minor functional disorders. I refer you to an article of mine published in the New York Medical Journal & Record of July—



page 25, "The Value of Quinidine Sulphate in Cardiology" I think quinidine is one of the best things we have had added lately to our resources in treating heart disease

The third remedy is theobromine and sodium salicylate (Merck) I use the five grain compressed tablet, with definite instructions that it should be taken after meals as fully as possible dissolved in half a glass of water You cannot give satisfactory doses of this remedy unless it is well dissolved in water because it has an irritative action on the stomach when it reaches the lining in concentrated form I have found this a very important point in the use of this most valuable drug In five grain doses three times a day, taken over long periods of time, it is of much use in eliminating the recurrence of anginoid attacks I have already referred often to the late Professor J M Groedel of Bad Nauheim This is because I studied so much with him and got so much valuable help from him It was he who taught me the use of this drug in this way Never forget the value of the salicylate in diminishing cardiac pain

The fourth remedy is nitroglycerin Again, we are up against the difficulty of unsatisfactory preparations I am told that Burroughs-Wellcome no longer make tablets as they find it utterly impossible to keep them satisfactorily My own solution of the problem has been to have granules representing  $1/225$  of a grain made with a solid coating These, I know, retain their strength for long periods of time because a good many people with recurrent anginoid pain test them practically every day In these

small doses nitroglycerin is a very useful remedy in almost any cardiac emergency It never does any harm and relieves many symptoms even where it is hardly possible to explain the reason So it is my custom to have nearly all people with important cardiac impairments carry a small phial of these granules for use in any emergency

The fifth remedy, without which I would not care to practice cardiology, is castor oil I try to train all cardiopathic individuals to take a full dose of castor oil at least once a month It is an insurance against the intestines becoming a depository of residual food matters and many people enjoy the sense of well-being which they feel after the monthly dose of castor oil In the face of very serious cardiac impairments I have found serial doses, say an ounce every other day for three doses, a very useful approach, particularly where saline elimination has been previously abused The constipation following castor oil is of advantage in the restoration of circulatory tone in some "down and out" individuals

If I had to deal today with a bad example of cardio-vascular renal disease with high blood pressure, badly disordered metabolism and failing circulation I would be apt to send them home with the following prescription

Rx Tr Iodine m XL  
Menthol gr VIII  
Oil Ricini 5 IV

Two tablespoonsful at night in orange juice, March 7th, March 9th, March 11th, March 18th, April 1st, April 22nd, May 22nd and then once every month

The relation between cardiology and gastroenterology is so intimate that if you scratch the skin of the cardiologist you will find underneath a student of gastroenterology. Cardiac function and gastroenterological function are so intimately associated that the medical mind cannot consider one without the other and the lay man usually confuses the two. I honestly think more people suffering from functional cardiac pain go to the gastroenterologist than to the cardiologist during the early stages of their complaint. I know of a newly established gastroenterological clinic whose first six applicants for treatment were suffering from cardiac disease.

In mentioning psychotherapy I do not wish to imply that we are in any sense suggesting the formal adoption of it in cardiology as it has been adopted in neurology but I do think it must always be considered as an important element in dealing with the heart sufferer. There are some principles of psychotherapy that we cannot get away from. In the first place, the minute we indulge the vice of prophecy of evil in allowing ourselves to fix even the idea of a failure of our efforts to cure we defeat the possibility of a successful psychotherapy. So prognosis must be in a large measure eliminated by the successful practitioner of cardiology. I say to people, "I hope and believe that my efforts will be successful in helping you. I do not know what the outcome will be. I have seen many people much sicker than you are do very much better than anybody had a right to expect." Personally, my

method has been to acknowledge frankly the danger of sudden death in serious cardiac disease. I say, "it is true, you may die suddenly, but of the great multitude of people with heart disease the number who die suddenly is very, very small. The sudden death of a prominent person on a golf course is advertised in every newspaper in the United States, and yet this happens only once in a few months. I cannot assure you that you will not die suddenly. I want you to accept it as a possible fact and then forget it."

This method of meeting the situation may be a matter of personal success on my part but it has always worked out very well and I never hear again an expression of the fear of sudden death. If I attempted by prevarication and dissimulation to conceal danger that is a fact I believe that the situation would naturally be aggravated. Here I must leave the subject to psychotherapy.

When I say that physiotherapy was the thing that led me to devote myself to cardiology it is easy to believe that it has always been a matter of the greatest interest. At the very beginning of this line of work I went to Bad Nauheim and studied the methods there and I think I absorbed certain principles that have been an influence every since. Physiotherapy involves the training of people as to exercise. My favorite prescription for heart sufferers is to walk out of doors before twelve o'clock in the day, up to the point of fairly definite physical fatigue. The principle that exercise should be taken before the work

of the day and not after is an important one. The business man who attempts to take exercise after his day's work does not get much benefit from it and usually gives it up. The man whom you can persuade to take exercise in the early morning gets the real benefit. Baths, exercise, light and electricity must all be considered but cannot be more than mentioned here.

I first became interested in cardiology through the work of men who were decidedly outside of the pale of the more conventional group of physicians, men who at that time were under the cloud that then hung low over the practice of physiotherapy. Most conspicuous among those was Dr. Schott of Germany and Bezley Thorne of England. These men held out hope to the heart sufferer.

The great modifying influence on the outcome of a cardiac lesion is re-education. The training of the individual to adapt himself to his capacity and surroundings. I prefer to treat people without removing them from their usual surroundings. A person cured without transplantation is in a much better position than a man who is sent away and then must come back to take up the burden of life. Of course, it is much easier in every way to re-educate a person if he can go away to a cure resort. Much benefit in this direction is obtained by people who go to Europe. Up to the present time we have no well developed cures in this country.

I wonder how many of you have ever considered the difference between private and public practice in cardiological work. By public practice I mean all that work done in hospitals,

dispensaries and teaching institutions and upon the poor or pauperized classes. By private practice I mean work that is carried on with people with whom the relationship of private physician is established.

In public practice one encounters a group of people many of whom have developed heart disease under conditions of irregular living and the strain of continuous labor, or who have lived under bad hygienic conditions. Also, a group of people who as a rule do not regard minor discomforts and who are in a great measure fatalistic in their outlook upon life.

In private practice we often have just the reverse. We have people who develop cardiac disease under conditions of luxury and indolence, a group that do not disregard any personal discomfort and who can and will carry out any reasonable plan of treatment or change of environment.

In the former group severe organic disease is very conspicuous. In the latter group functional disorder predominates.

Then, of course, the man who draws his experience chiefly from hospitals must constantly have a great deal to do with the end results of an unsuccessful attempt to adjust heart sufferers to this environment. In public work the personal relationship of the physician may also carry with an unconscious but helpful psychotherapy but details of adjustment of diet, exercise and education in the use of drugs are lacking. There are many individuals in the public practice group who are invalids on account of the lack of adjustments but who,

if in the private practice group, would pursue active and useful lives

The practice of cardiology which I am attempting to describe at this time pertains only to the private practice group. Success in the treatment of the cardiopathic person depends upon personal relationship in a great measure. This was very much impressed upon me as a young physician when a member of the family of one of our greatest physicians came under my care one summer and after much detailed attention I was fortunate in improving her condition. This happened in the summer, a long distance from New York. When I returned in the Fall I expected, of course, that the doctor would become her principal adviser as he was very fond of her. He reviewed the whole situation carefully and finally when I met him he said, "I want you to go on with this case. I will give you every help that I can, but it is a one-man case and I think that my cousin will do much better if I do not treat her." This taught me a great lesson in the practice of cardiology, that a serious heart problem is a one-man problem and valuable as the consultation or conference is, the heart patient is much better for the well considered and well advised counsel of a single physician.

If therapeutics were a definite, clear-cut science it might be directed by a jury but the man who has developed a therapeutic sense often wishes to do things which he feels to be best but which he does not do if he can only do so after the effort of persuading a jury of physicians to agree with him. The good therapist

often wishes he could give a single dose of a remedy to study the reaction of the person in his charge, planning his next dose upon the effects of the first dose, and so on. This is impossible when working with a jury.

Public cardiology is the practice of cardiology carried on in front of a jury, and in large institutions a pretty large jury, at that, including nurses, doctors, students, other patients in the ward and friends and relations.

The heart patient treated by one good doctor gets full and adequate treatment. With two doctors he gets what those two can agree upon and I have never yet seen an adequate, complete therapeutic plan come out of a conference of half a dozen consultants. The best results are reached when, if the physician finds himself insufficiently trained for the care of his patient, he associates with himself a cooperating consultant who carries the work along with him and the two, together, work out a continuous and logical plan. The time element in assimilating all the points of a difficult medical problem is important and the second conference in a serious situation is often much more productive of results than the first.

The proper practice of cardiology involves the continuous care of people. It has no place to my mind in that type of practice which constitutes prescribing for people for the cure of what they complain of at the moment for the relief of symptoms. This type of practice is demanded by the masses and is necessarily a legitimate activity of many practitioners but it has no place in serious cardiac disease.

There is no use in attempting to do good work in cardiology except under conditions of continuous observation. The true cardiologist is a very poor consultant. He cannot work quickly enough or complete his task well enough at one interview. The single interview consultation is much better carried on by the general medical internist. If the cardiologist is employed in a case he should be employed for continuous association. Otherwise this special training is pretty much wasted.

A follow-up of patients according to the methods recommended by many good thinkers and set forth not long ago in a pamphlet by Dr Niles of the Cornell clinic is a great help.

In this sketch of the practice of cardiology as it has grown up and developed it has been necessary to

omit all consideration of the theories and care of arteriosclerosis and of the many frequently occurring complications that come to cardiopathic subjects. In general, however, the best results are accomplished when heart, blood vessels and kidneys are considered as parts of one mechanism which cannot be considered apart from the brain, stomach and general nervous system. Also, everything must coordinate with a due regard to the personality of the man or woman whose life, health and happiness are to depend upon our efforts.

If I have presented an ideal picture of the practice of cardiology it is what I intended to do. Throughout I have enjoyed the sympathetic help of many in this association and I bespeak the same for all earnest workers in this special department of the healing art.

# The Relationship of Precordial Stress, Blood Uric Acid, and Salicylate Therapy

By MILTON A. BRIDGES, B.S., M.D., F.A.C.P., *New York Post Graduate Medical School and Hospital, New York*

A PERIOD of years ago, as the result of a fatality from angina pectoris, in a male thirty years of age, sufficient stimulation was produced to attempt to seek out further enlightenment concerning this much discussed entity.

This angina pectoris fatality occurred in the instance of a case that had been thoroughly investigated to the best of the available resources. This investigation consisted in several associated physical examinations, electrocardiographic tracing, complete chemical blood analyses, urine analyses, and basal metabolic determinations together with cardio-pulmonary roentgen examination. In addition, consultation of the highest calibre had been obtained. The only finding, physical, chemical, or otherwise, which differed from normal, was that of a mildly elevated uric acid.

Following the above incident, perusal of both private and hospital records was made of all patients that had complained or still complained, of precordial stress. This large group of cases was still further restricted in so far that out of all the cases of precordial stress only those in whom a blood uric acid and blood urea had been determined were selected. In

addition, further restriction was made in selecting only those cases in which blood urea nitrogen was considered relatively within normal limits.

Careful perusal of this series showed it to be noted that the mean uric acid reading was 4.77 mg per 100 cc of blood. A corresponding series of uric acid readings of an equal number of cases selected indiscriminately, with the exception that precordial stress cases were omitted, yielded a mean average of 3.1 mg per 100 cc.\* In order to anticipate within reasonable bounds, any error in laboratory technic, the majority of the blood determinations were made in two laboratories, one of which was connected with a large private hospital, the other was a private laboratory under recognized supervision. The respective findings were frequently duplicated in a number of cases by part of the same specimen being sent to each laboratory.

In the light of the immense variation as to consensus of opinion in relation to normal blood uric acid determination, a survey of the vari-

\*Bridges, M. A.—"Blood Uric Acid and Precordial Stress," *Medical Times*, October, 1926.

ous determined normals at different institutions throughout the country was made, with the result that the acceptance of 3.3, as being the upper physiological limit was determined upon

Considering this figure of 3.3 as the upper limit of a normal reading it was deduced that in cases of precordial stress there tends to be an elevation in the blood, above the upper physiological limit, of the uric acid reading

No attempt was made, in the light of the meagre information presented at that time, to establish any definite conclusion in relation to the findings. However, some vague association between blood uric acid and the symptom of precordial stress was suggested

Since the publication of the material calling attention to this association, consistent accumulating records have been kept of various cases coming under observation, and an elevated blood uric acid has been almost constantly found in cases presenting the diagnosis angina pectoris vera. This observation concerning uric acid has been used in various instances in differentiating between the false and real angina pectoris cases, concerning which confusion in diagnosis might have occurred

With this material at hand, an explanation of the relationship was neither vouchsafed nor possible with any definite feeling of assurance. Consultation with colleagues suggested that an effort be directed at the reduction in the blood of the uric acid reading and observations be made of the resultant effect upon the symp-

toms. At the present time this report presents a series of cases which have been under close observation over a considerable length of time in whom anti-uric-acid therapy was instituted

Appreciating full well the medical haze, particularly in the minds of the most eminent cardiologists, which is associated with this far from clear entity, precordial stress or angina pectoris, efforts were made in each of the cases under treatment to have the opinion of at least one recognized cardiologist in substantiation of the presenting diagnosis

Each case of the entire series, which number nine, was observed under practically the same regime. In no instance was hospitalization, in the sense of confinement to bed or prescribed periods of rest, etc., instituted. In all but two instances, each individual was allowed to continue at his customary daily occupation. The diet in each case was grossly purin free. The medications were salicylates in watery solution, or with an inert menstruum, or various of the phenylchonic acid group. In the earlier cases of the series, dating 1923, the latter form of therapy was utilized. In the latter part of the observation, salicylates were used. In no instance was any further medication of any type or description administered other than in one or two cases, in which amyl nitrite ampules were used for the more severe attacks

Realizing the conventional difficulties in presenting the pertinent details in such a series of cases, our intention is to sketch only briefly the salient features of each case as follows

acid group was instituted, consisted in administering the medication in doses from 10 to 40 grains once to three times daily, in the middle of a meal. In the earlier cases, the medication was prescribed directly after meals, but it was found that the gastric tolerance did not admit of even moderate dosage, and hence the former suggested mode of administration was instituted.

In reference to the salicylate therapy, sodium salicylate was utilized, and the preferable route was decided as being per rectum. The dosage varied from 100 to 400 grains of sodium salicylate in a 50% aqueous solution, mixed with between 2 to 4 ounces of thin starch paste. This preparation was administered as a retention enema, immediately prior to retiring. The frequency of administration in several of the cases was nightly, in others, every second night. In one instance rectal intolerance was exhibited, showing itself in the inability to retain the enema.

Various combinations of rectal and oral administration were prescribed. Owing to gastric intolerance, at no time was over 40 grains of sodium salicylate administered by mouth. In all cases treated with salicylates, after the second or third day, tinnitus was complained of. On the presentation of this symptom, the dose was either moderated, or discontinued. In no instance, after rectal administration, were there any disturbances complained of. The only disturbance was a salicylate rash. In two instances a transient aciduria was to be noted, which completely disappeared upon moderate

or cessation of therapy. Haematuria, gross or microscopic, did not ensue.

Contrary to the prevalent opinion in reference to the deleterious effect salicylates are supposed to have upon the hemoglobin, in so far as it is supposed to be reduced under severe or prolonged administration, in all instances a casual Tallquist hemoglobin reading presented a gradual increase in the same.

Universally, upon the cessation of cardinal symptoms, the therapy was reduced in both quantity and frequency, the diet still maintained, and in those patients still under our professional care, no medication of this nature whatsoever has been administered since a moderate period following the cessation of their attacks.

The entire series of cases are non-selected ones, which have come for observation under routine office and hospital practice. No attempts have been made to select those presenting a spectacularly high uric acid reading, or any other differentiating characteristic.

In each of the above noted cases, having been treated in having at least one, the majority of cases confirmed the reputation of salicylates as a remedy for the disease.

It is  
S. C. L.



*Initial uric acid reading*—4.8 mgm per 100 c.c. of blood

*Initial Urea N*—10.2 mgm per 100 c.c. of blood

Severe clinical case of angina pectoris, with ten to fifteen attacks daily

*Progress*—Eight days after institution of treatment, uric acid reading 1.4 mgm per 100 c.c. of blood

Subsequent uric acid reading, nine months later—3.0 mgm per 100 c.c. of blood and 11 months later 2.0 mgm per 100 c.c. blood

This case was judged to be sufficiently severe to warrant hospitalization, and such was instituted without bed restriction

Since the cessation of attacks eight days after institution of treatment, patient has had no recurrence to date, of original symptoms

*Therapy*—The treatment consisted in salicylate saturation

#### *Case "F C"*

*First Observation*—April 1927

*Sex*—Male

*Age*—54.

*Initial uric acid reading*—3.5 mgm per 100 c.c. blood

*Initial Urea N*—17.4 mgm per 100 c.c. of blood

Complete clinical and historical picture of angina pectoris, with frequency of ten to twelve attacks daily

*Progress*—Upon last professional association, May 1927, patient was experiencing one attack a day

Due to intolerance to therapy, other professional service was retained in home town

*Therapy*—Salicylate saturation

#### *Case "O.D."*

*First Observation*—April 1927

*Sex*—Male

*Age*—61

*Initial uric acid reading*—4.2 mgm per 100 c.c. blood

*Initial Urea N*—14.0 mgm per 100 c.c. blood

Clinical picture of angina pectoris with frequency of attacks two to three weekly

*Progress*—One month later, complete cessation of attacks

Symptom free to date

Eight months later, uric acid determination—2.3 mgm per 100 c.c. of blood

*Therapy*—Moderate saturation with salicylates

#### *Case "J H"*

*First Observation*—June 1927

*Sex*—Male

*Age*—55

*Initial Uric acid reading*—3.2 mgm per 100 c.c. blood

*Initial Urea N*—13.3 mgm per 100 c.c. blood

Clinical and historical picture of angina pectoris, with frequency of 25 to 30 attacks daily

*Progress*—Complete cessation of attacks two weeks after institution of treatment, uric acid at that time—2.1 mgm per 100 c.c. of blood.

No recurrence of attacks through the concluding two months of observation

Clinically the patient also complained of a definite intermittent claudication, which abated coincidently with the cessation of the cardiac syndrome

*Therapy*—Moderate salicylate saturation

#### *Case "L W"*

*First Observation*—October 1927

*Sex*—Male

*Age*—67

*Initial uric acid reading*—4.0 mgm, per 100 c.c. blood

*Initial Urea N*—13.65 mgm per 100 c.c. blood

Clinical and historical picture of angina pectoris, with frequency of two to three attacks daily

*Progress*—Cessation of attacks approximately two weeks following institution of treatment, with a co-incident uric acid determination of 2.1 mgm per 100 c.c. blood

No recurrence of attacks during subsequent observation of six weeks

*Therapy*—Moderate salicylate saturation

The general management of the treatment when the phenylcinchonine

acid group was instituted, consisted in administering the medication in doses from 10 to 40 grains once to three times daily, in the middle of a meal. In the earlier cases, the medication was prescribed directly after meals, but it was found that the gastric tolerance did not admit of even moderate dosage, and hence the former suggested mode of administration was instituted.

In reference to the salicylate therapy, sodium salicylate was utilized, and the preferable route was decided as being per rectum. The dosage varied from 100 to 400 grains of sodium salicylate in a 50% aqueous solution, mixed with between 2 to 4 ounces of thin starch paste. This preparation was administered as a retention enema, immediately prior to retiring. The frequency of administration in several of the cases was nightly, in others, every second night. In one instance rectal intolerance was exhibited, showing itself in the inability to retain the enema.

Various combinations of rectal and oral administration were prescribed. Owing to gastric intolerance, at no time was over 40 grains of sodium salicylate administered by mouth. In all cases treated with salicylates, after the second or third day, tinnitus was complained of. On the presentation of this symptom, the dosage was either moderated, or the frequency diminished. In no instance during rectal administration, were gastric disturbances complained of. In no instance was a salicylate rash exhibited. In two instances a transient albuminuria was to be noted, which completely disappeared upon moderation

or cessation of therapy. Haematuria, gross or microscopic, did not ensue.

Contrary to the prevalent opinion in reference to the deleterious effect salicylate are supposed to have upon the hemoglobin, in so far as it is supposed to be reduced under severe or prolonged administration, in all instances a casual Tallquist hemoglobin reading presented a gradual increase in the same.

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The entire series of cases are non-selected ones, which have come for observation under routine office and hospital practice. No attempts have been made to select those presenting a spectacularly high uric acid reading, or any other differentiating characteristic.

In each of the above noted cases, we have been fortunate in having at least one, and in the majority of instances, several consulting confirmatory opinions by physicians of repute in order that a substantiation of the diagnosis could be initially instituted.

To date we are pleased to observe that of those cases still under our observation there has been no recurrence of the original presenting symptoms.

#### SUMMARY

1. In a series of nine consecutive cases, suffering from angina pectoris, the mean uric acid reading was estab-

lished as being at or above the upper physiological limit

2 Confirmation of the diagnoses was established by qualified consultation

3 Therapy was directed at the reduction of the blood uric acid

4 In all cases, complete cessation of symptoms was accomplished within a shorter or greater length of time following the institution of treatment, depending upon the mode of therapy

5 In all cases definite response in the reduction of the blood uric acid readings was noted

6 The hemoglobin determination in all cases presented a slow but gradual increase

7 In several cases, a transient albuminuria was encountered

8 In no instance while under observation, have any of the cases recurred in reference to symptomatology

9 At no time were any untoward salicylate permanent effects noted

### CONCLUSIONS

In dealing with a subject of such great import as the one under consideration, and bearing in mind the

marked amount of investigation and research of one form or another that has been applied to this entity, it would be far from becoming, upon the meagre information at hand, to offer any satisfactory or complete explanation for this grave medical condition

Conclusions should be more of the self-addressed query type, rather than dogmatic statements. Explanation, it is felt, cannot be safely vouchsafed for the results herein described. Certainly no assurance can be claimed that uric acid produces angina pectoris, and also no assurance is to be offered that in the reduction of uric acid rests the cure for this often fatal entity. It is barely possible that some undetermined element in the blood, a product possibly, of faulty metabolism, might be the chief offending factor which precipitates this distressing cardiac syndrome

Suffice to say complete alleviation has been afforded in each of the aforementioned instances, by the suggested therapy, with a coincident decrease in the blood uric acid reading

(Appreciation is expressed to Herman O Mosenthal, M D, and John A Killian, Ph D, for their co-operation in the above work)

## Editorial

### *MEDICAL OBSERVATIONS IN HAWAII*

#### *I Human Germ-Plasm Mixtures*

To the medical man who is interested in heredity and genetics the Hawaiian Islands offer a fascinating field for the observation and study of racial hybrids and mixtures. There are said to be at least thirty-seven distinct human mixtures of germ-plasm in Hawaii. One can well believe this and even consider the possibility of a much greater variety of mixed bloods. For two centuries, since the visit of Captain Cook to the islands in 1728, this germinal melting-pot has been in action, and the results of these two centuries in the production of well-defined human hybrids are amazing to any one who has passed his life, or the major part of it, in lands where the human population is fairly homogeneous as in the United States. Nature has been forced to a wonderful genetic experiment in Hawaii, and it would seem at first glance that here is a wonderful field for genetic study and conclusions. The opportunity for a scientific study, however, is not as promising as it appears to be on the surface, since the family histories are very unreliable, and inaccurate beyond the one single generation, and the peculiar habits of the natives and their hybrids in giving away and exchanging

ing their progeny lead to very heterogeneous family combinations. It is not uncommon to see in one family girls representing one hybrid and the boys another, and to have this explained as due to an exchange of excess girls for excess boys. In spite of those complications, however, there is a fertile field in the islands for human genetic study, and so far very little has been accomplished in this direction. It seems too good an opportunity to be untouched. The first impression of Honolulu is, of course, that of the Oriental character of the mass of the population, Japanese and Chinese, and their various hybrids predominate, the native Hawaiian and his hybrids is decidedly in the background and overshadowed by the Oriental. Only in the more distant rural portions as in certain parts of Kauai and Hawaii does one get an idea of the original native. His is a disappearing race, the number of pure-blooded Hawaiians is rapidly diminishing and the race is being lost in its many hybrids. The almost total lack of a sex-morality in this race has been its undoing, and the absence of any sense of racial purity and pride in race-preservation has led in these two centuries of contact with alien races to such mixtures and dilutions of its germ-plasm, that the race is doomed to extinction. As to the value of these hybrids opinions in

the islands differ somewhat, but the most commonly expressed one is to the effect that the Chinese-Hawaiian cross is the best of the hybrids and the Portuguese-Hawaiian the poorest. Conclusions based only on a three-weeks' observation are never safe, of course, but the editor would agree to this commonly-expressed opinion. As to the hybrids between native blood and that of Europeans and Americans first impressions and conclusions based upon them are perhaps dangerous but in general the impression of an inferior type of hybrid was formed, a lower morale and a greater instability of character and inferior physical development in addition. Some of these hybrids were of extraordinary interest—Irish-Hawaiian, Scotch-Hawaiian, Yankee-Hawaiian, etc., some personally attractive, especially the Irish mixture, but all of these hybrids that were seen were physically slender, slight and more or less weak in build. Sooner or later all revealed evidences of an inferiority complex based upon their inheritance of native blood. The impression made by all of them upon the writer was that these hybrids of Caucasians and Hawaiians were distinctly pathetic. As far as could be determined their resistance to some diseases is poor but higher to others. The native Hawaiian has a relatively high susceptibility to tuberculosis, but this susceptibility is lower in the part Hawaiians than in the natives. This increased resistance to tuberculosis may be gained from the Caucasian blood. On the other hand the great majority of new cases of leprosy developing in the islands were, at the time of my visit, in the pure Hawai-

ians and their hybrids, the latter in excess. As far as this disease is concerned, the susceptibility of the native to it seems to be passed on to its hybrids. The opportunities for drawing any conclusion as to the reaction of syphilis in the native race and its hybrids were few, but the few severe cases seen were in Caucasian-Hawaiian hybrids and not in the pure native. Skin affections of many kinds were noted in the native race and in its hybrids. In the report of Dr H W Chamberlin, Director of the Bureau of Tuberculosis, it was shown that for the last year the number of new cases and the number of deaths decreased among part Hawaiians, Filipinos, Caucasians and Spanish, but increased among Hawaiians, Japanese, Porto Ricans and Chinese. Koreans showed a continuing increase in the death rate, but a decrease in the number of new cases. The death rate for tuberculosis in the pure native Hawaiians was 410 per 100,000. There were 4176 cases of tuberculosis and 224 deaths from this disease in 1928. It is the most important single disease of the islands. Last year infant deaths constituted 24.1 per cent of the total mortality, the present year's death rate being 83.60 per 1000 births. In 1928 there were 44 cases of leprosy reported, a decrease of 23 from the preceding year. Diphtheria has been increasing in the islands during the last five years, in the past year there were 420 cases reported with 52 deaths. Special plans are under way for a campaign against these two diseases, including the better reporting of tuberculosis, and the use of anti-toxin. Eight cases of bubonic plague

were reported last year, there is an endemic center along the Hamakua coast in an area 20 miles long by 3-5 miles. As this tract is largely jungle it can be seen that the eradication of rodents (plantation rats) in the region is practically impossible. As of June 30, the estimated population of the islands is 348,767, an increase of 15,347. The birth rate has risen from 27.16 per thousand to 33.84 while the death rate has dropped from 11.87 to 11.70. Of the total population 228,276 are American citizens and 120,491 are aliens. The American from the States finds a certain difficulty in the recognition of the fact that the individual members of the 228,276 mixture representing hybrids of so many diverse races are his brothers—they are American citizens and very proud of that fact. One is naturally surprised to hear a dark combination of Hawaiian and Portuguese exclaiming loudly in an altercation with some other equally marked hybrid that he is a "white man," an "American." These people are quick to resent any implied suggestion of differentiation from the Americans on the "Coast." They resent also any suggestion from the outside as to the inferior value of certain hybrids, although they freely express their own views, and betray certain strong class, or rather racial, antagonisms and prejudices. Nevertheless this does not keep them from intermarriage with the other race when the individual desires such a union or finds it convenient. In appraising the value of the hybrids of the Caucasian and Polynesian or Oriental races it must be borne in mind that many of the

white fathers were whalers, sailors, beach-combers, derelicts, etc., and the value of the resulting hybrid is largely that of individual heredity rather than of racial values. There is much to be said on the other side about the racial mixtures in the Islands. Common courtesy or politeness is much more evident on the streets of Honolulu, particularly in the Oriental quarters, than in any American town or city. All of these hybrids with very few exceptions present a cheerful, smiling face, they are clean and dressed in clean fresh clothes—I saw only one dirty person in the three islands visited. They are fond of children and passionately fond of flowers. Their small simple shacks are surrounded by flowers and food-bearing trees, and the great majority of them show the possession of a well-developed esthetic sense in the use of flowers about their homes. In this respect they are far ahead of the average rural inhabitants of the States. Children are everywhere—Chinese and Japanese families of 6-8-12 or more—smiling, clean and well behaved and living under economic conditions that could not be successfully met by the American without succumbing to dire poverty, degeneracy and disease. In spite of all this pleasant outward picture the medical mind sees beneath these attractive pleasant childish countenances too many evidences of insufficient nutrition. They are almost all anemic, show a distinct pallor and nowhere in the islands was a rosy-cheeked child visible. The same is true of the white children there, so that climatic factors are responsible to some extent. The problem

of under-nutrition is of course most marked in the case of infants, and the latter show the economic deficiencies much more than the older children. The medical visitors to the Islands returns to the States with mixed feelings centering chiefly about the problems of human hybridization and its ultimate result, and the effects of a low economic status upon the vitality and future development of the hybrid products of diverse races.

### *DEDICATION OF THE MEDICAL CENTER, NEW YORK*

The dedication of the new Medical Center of New York is an event of great interest to all teachers and practitioners of medicine in the country. Dr. Lambert's address on this occasion contains so many points concerning the future of our profession that we consider it worth while to reproduce it here. Although inspired naturally by the local conditions it has a broader relation to the whole field of medical teaching and practice throughout the United States, and we reprint it primarily because of its broader significance. Both the teaching and the practical sides of Medicine are in a state of great instability at the present moment and the future of each is difficult to read. Any great local event in the development of medical schools is of great importance to the country as a whole.

#### HOSPITAL CLINIC AND MEDICAL SCHOOL

By Samuel W. Lambert, M.D.

On this occasion of mutual congratulation for Hospital and University it is my pleasant task to present

the medical significance of the amalgamation of school and clinic under one roof. These buildings typify the ideals and dreams that have stimulated the teachers of medicine of the College of Physicians and Surgeons in their work for many years. I appreciate to the full the honor which has been done in delegating this opportunity to me.

The Presbyterian Hospital founded in 1868 represents the humanitarian impulses of one of the Christian Churches in this City to carry out its whole duty to the poor of New York without regard to their creed, nationality and color. It is a direct descendant of the sanatoria of Greece which developed from the Asclepieia or temples of Aesculapius, and of the hospitals which begun by the Crusaders of the 11th century spread over all of Christian Europe in the following 200 years. For forty years the Presbyterian Hospital was one of the big four in this City, its attending staff included the leaders of the profession, in fact it divided the time of its physicians and surgeons in a friendly way with some of its fellow institutions. Such was the habit of the day. The Presbyterian Hospital was always a leader in granting to its medical board the best of facilities for the care of the sick and opened its wards for the teaching of students to any extent that was requested by its attending medical and surgical staffs.

The College of Physicians and Surgeons was founded in 1807 under the auspices of the Medical Society of the County of New York, as an effort by the organized profession to

improve the methods of teaching then in practice in their City. It was a rival of the existing Medical Department of Columbia College. This new School was a success from the start, and in 1813 absorbed the medical faculty of the College, and Columbia went out of business so far as medical education was concerned for some 75 years. In 1890 the faculty of the College of Physicians and Surgeons saw the error of its way as a proprietary school, appreciated the trend of medical education and was among the first of the great proprietary schools of the Country to establish a university connection and merge its corporate existence in Columbia University. As the Chairman of the Board of Trustees of Columbia University has just said, this convocation will commemorate the logical results of these endeavors of the past and dedicate this latest development of a university medical school combined with a group of hospitals into a great medical center. This example is soon to be repeated and medical education in New York will be the gainer, and this Columbia-Presbyterian Hospital foundation will also be the better for the friendly rivalries which will follow the growth of the second medical centers now being planned for by the Cornell University-New York Hospital authorities.

The science of medicine is not an exact science governed by laws and rules of mathematical accuracy. Rather it is empirical, founded on experiment and experience. The practice of medicine has to consider too many variables in the application of its theories and its art ever to become

fixed and unchangeable. Medicine deals with the living bodies of man and its living cells, and with the living germs of disease. It concerns itself with the antagonism of the one group of cells contesting with the other group of cells. When the cells of the human body are in the ascendant the result is health, when the bacterial or other noxious cells are triumphant, the result is disease. Medicine is concerned with the chemical toxins of disease and the chemistry of the organic and inorganic poisons of the vegetable and mineral world. Medicine has to consider the varying resistance to disease of the human organism and equally the influence of the changing virulence of the bacterial causes of acute infections. All the facts having to do with these medical problems are as yet undiscovered and in consequence medical science is constantly changing the theoretical explanation of observations which are noted in the laboratory by the scientific worker and at the bedside of their patients by the practitioner of the clinical art.

The soul of the medical school and hospital is the medical clinic and every specialty is an offshoot and growth from it. The organization of a medical clinic today is very complicated. The internist is the governing personality but the hospital is no longer in the hands of a single medical practitioner, the medical staff consists of a chief and several grades of associates and assistants whose work is distributed through the wards and the clinic for ambulant cases. No distinction is made between the patient in the hospital and the patient in the



dispensary The record of the patient's illness is a unit whether he be under treatment in the dispensary which should be considered his regular medical adviser or in a bed in the ward the use of which is an incident in the course of his disease to be occupied by him only when too ill to be treated at visits to the dispensary and as such intervals as may be necessary This medical staff who have control of the determining of the diagnosis and of directing the patient's treatment are assisted by the many scientific departments whose work is subsidiary The medical clinic must have its department of chemistry to investigate the conditions of digestion, of the blood, and of the secretions, its department of physics to apply electricity in the form of X-ray or of the electrocardiograph, a department of physiology to study the complicated actions of the internal secretions of the body, a pathologist to furnish the results of microscopic examination of secretions and diseased tissues removed from the patient for diagnosis, and a bacteriologist to supply cultures for diagnosis and anti-toxic serums for therapeutic purposes The activities of a medical clinic are not limited to the care of patients The hospital staffs of today devote a large amount of time to experimenting with the phenomena of health and disease, and to the end that the diagnosis and treatment of those ill is improved not only in the clinic of the investigator but throughout the entire medical world The medical clinic must be in charge of a staff of diagnosticians who can correlate and employ the results furnished by

their various subdepartments of science The diagnosticians must be more They must also be teachers who can understand the mental processes of the beginner and get down to the level of the medical student, to meet his doubts and difficulties not only with appreciation but in a sympathetic way The reputation of the medical clinic in any combination of school and hospital is still the chief factor which determines the choice of the school by a prospective student Forty years ago there were three large medical schools in this City as there are today and the medical student of that day was attracted to each in accordance with his desire to be taught by a Delafield, a Janeway or a Loomis One thinks today of Munich as a center of medicine in terms of Friedrich Müller, and formerly as the professional home of v Ziemssen One thought formerly of Vienna as the site of the clinics of Skoda and Bamberger, and now as that of Wenckebach Paris reminds the medical man of the work of Louis and Widal

Much has previously been said of the methods of teaching Today there is but little difference in the methods employed in Germany, in England, France or the United States Methods are far less important than the personality of the teacher When I last visited Munich I found Müller teaching the rudiments of physical diagnosis to his youngest students Theodore Janeway held a medical clinic in this College, also for second year men The American schools of medicine were the last to adopt modern methods of education But when

the schools were at their worst the students of medicine could secure the best of training at the bedside in the hospital from private preceptors who were up-to-date long before the medical schools appreciated what was going on. When the reform came it came from within the profession itself and the elimination of the weaker schools by consolidations and discontinuance has reduced the number of schools in the United States from one hundred and sixty odd to eighty. This improvement in medical education was helped by the drafting and passage of medical practice acts which have formulated conditions and requirements for licensure.

*The curriculum of every medical school can unquestionably be improved. The control now held over it by law is too fixed and inelastic. The administration of the law by state departments could well be limited to the examination of the graduates of the schools and give less time to the oversight and enforcement of a measure of education by the yardstick of time devoted to a study rather than to a measure of the result attained in acquiring knowledge.*

The youngest medical student cannot begin too early to discover that the diagnosis of disease is not a simple problem in mathematics. No two human beings react exactly the same to the same infection. The medical student should see at the bedside what pneumonia patients look like at the same time that he is studying the diseased lung and the method of growth of the causative bacteria in the laboratory. He should be able

to correlate the surgical treatment of fractures with his study of anatomy.

These buildings of the Medical Center present the latest fulfillment which has been built to carry out the complex requirements of an art and a science. Every necessary detail has been supplied for the medical clinic and similar facilities have been furnished for surgery including urology and for obstetrics. Under the same roof all the activities of the College of Physicians and Surgeons also are housed and provided for. The Neurological Clinic and the Babies Hospital have become integral parts of the Medical Center, and have built partly separated buildings and preserved a separate board of managers. The details of incorporation may be different so long as the unity of interest in medical education is preserved.

*The organization of the Medical Center cannot be considered complete until every specialty of medicine and surgery including the Crocker Special Research Laboratory has not only its dispensary but also its wards for the care of its patients when treatment in bed is required for them.*

This center for medical training is so well conceived and developed that it seems an untimely criticism to suggest that anything is lacking. I cannot refrain, however, from calling attention to a necessary addition which will round out the professional life of the students and instructors, especially the younger workers in the hospital and clinical laboratories. It is full time that some university shall make provision for the home life of the students of medicine. It

would be an innovation but it would be a great help to foster a professional spirit among them if dormitories and a common dining-hall can be added to the group of buildings which are being planned for and developed upon this site. It is timely that medical students who devote at least two-thirds of every twenty-four hours to study and practical work in securing a medical education should be furnished with a physical means of leading a life in residence in more or less intimate social associations with the younger enthusiastic instructors outside of their professional intercourse. *I do not expect or suggest that such an addition to the medical center would lead to anything approaching a cloistered life. On the contrary medicine today cannot be shut up in any monastic enclosure and no group of physicians who are teachers can eliminate from their professional activities a contact with the outside public without losing a broadening and enlightening point of view.*

The profession must be careful not to lose its influence on the rapidly developing activities of sanitation, and preventive medicine. This Medical Center contains the germ of such a department supported by the endowments of the De Laman bequest. Activities in Public Health are being carried on throughout the world in a most efficient manner under the support of special philanthropic foundations and the universities are threatened with a loss of what should be one of their chief services to the public. *What is true of the Medical Center as a whole is equally true of*

*every individual in it from the highest to the lowest and there should never be promulgated a regulation or law of the university or hospital, which will prevent any appointee on the medical staff from devoting what time he may to extra mural work connected with his profession. His work in education in the medical center must always be his chief occupation and this is a question for each individual to decide for himself, and as he may choose either to abstain from or to undertake such duties he should be neither restrained nor compelled in the freedom of his choice. The clinical teacher who is an active investigator in a laboratory will be the better for an experience in practising the art of medicine outside of the walls of his hospital even if that experience be a limited one both in time and in amount, and the medical consultant who is a teacher must have had an experience in the technique and atmosphere of the scientific laboratory if he is to give his students the best that is in him.*

The old method of constructing a hospital spread out over a large plot of land in separate pavilions has been changed into this newer one of superimposing one pavilion on another and utilizing the air spaces above the ground,—I had almost said the heavens above. As far as the variety of scientific languages that are to be spoken here are concerned this is a veritable Tower of Babel but in that fact lies not its disunion but its firmest foundation. In the point of view of medical administration the dispensary of Vanderbilt Clinic will become

not only the admitting office but the discharging office, not only the distributing office but the executive heart of the whole institution. In it there will be a department for every specialty even of those allied institutions which are building on adjacent plots their own hospitals for specialties which have not been included in the original plant and which will have to be represented by ambulant clinics within the walls of the Vanderbilt Clinic. The dispensary in the modern conception of a medical center is the controlling factor of the whole. *The medical center is recognizing as a branch of medicine the closely allied specialty of dentistry and the inclusion of the school and clinic for dental and oral surgery marks a new departure in the organization of a university school of medicine.*

One of the latest developments in medical education has been to recognize that a school of a certain size can educate only a certain number of students. The old method of unlimited admission of as many students as may apply and of trying to teach medicine to them by theoretical lectures alone is dead. A medical teacher also cannot be required to repeat his instruction to groups of students going over the same work too frequently, destroying his initiative, and converting a useful scientist into a mechanical performer. What number of students shall make up an educational unit for any school will depend on the size of the hospital rather than on the size of the laboratories because separate groups of instructors can be rotated in the same laboratory rooms on different groups of

students while the clinical staff of a hospital cannot be changed periodically without detriment to the care of the patients and the development of medical science in the hospital. *New York City contains many hospital plants which are manned and equipped for teaching purposes and which are used but little for the purpose. No hospital can fulfill its complete purpose or develop its full power unless it adds some system of education to the active work of the medical staff. Whether the future for these hospitals lies in devoting themselves to graduate instruction or whether any of the existing medical schools can find a solution by effecting alliances with more or less distant hospitals to benefit both the university and the independent hospital depends upon the future organization of medical education. It would seem a shame that the facilities of New York for education which are now neglected and unused should not be better employed than at present. One thing is certain, it is not good for undergraduate students to receive their only impression of clinical medicine from a single institution or from only one instructor, however brilliant he may be. Different minds work in various methods in reaching conclusions in medical diagnosis and treatment. The teacher with a logical and mathematical mind will present to his students a more exact picture than will the diagnostician of the imaginative and artistic type, and yet both may be successful in medicine for both must be artists to succeed in the art of medicine, and imagination is not necessarily lacking to a mathematician.*

Alice experienced her adventures in Wonderland in the imagination of a successful student of mathematics

Medical education demands six years preparation before eligibility to practise is acquired and it should be demanded of every student further that he have one year of hospital internship before he is accepted by the State for licensure. It would seem wise that this extra year should be under the control of the school rather than the State, and it is no new thing to suggest that the degree of Bachelor of Medicine should be rehabilitated and given at the end of the present medical course and that the degree of Doctor of Medicine should be reserved to a hospital graduate after at least one more year of supervised medical training.

American medicine began and was built up in the spirit of scientific doubt and investigation first preached by the ancient school of Greece. These ideals were inherited from the London of Sydenham and the Leyden of Boerhaave, through the teaching of Cullen in Edinburgh and of John Hunter in London. It was developed by the spirit of France in the personalities of Bichat, Laennec, and Louis. It was made scientific by the genius of the Germany of Johannes Müller, Virchow and Ludwig. It inherited its methods of teaching from all of these and they were crystallized especially through the clinics and laboratories of Vienna of Neusser and Kolisko. *The College of Physicians and Surgeons has built up its own traditions through its pioneer physiologist Dalton, its clinician and pathologist Delafield, its surgeons Parker,*

*Sands and Bull, its exact and critical scientist Prudden, and its anatomists Sabine and Huntington.* The spirit of commercialism has never yet tarnished its reputation. The discoveries of its laboratories and its clinics have been free to all the world. It may seem strange to emphasize such a fact which should be self-evident but in these days the seductions of the patent office have led more than one university professor into practices that the profession of medicine has always shunned and should continue to condemn. The future of this School is assured if it is never forgotten that it is a school of medicine, that its scientific departments should be in the hands of chiefs who are first doctors of medicine and scientists in addition. In making this statement I do not forget the epoch-making work in medicine of the chemist Pasteur. He is the exception that proves the rule, and every time that this rule is broken the burden of proof as to the wisdom of its act, is placed squarely upon the shoulders of every medical faculty which dares again to make an exception. *Every department in this medical center must be scientific but it must not happen that the scientific spirit shall destroy the clinical spirit. The fact must be remembered that the hospital and the school are working for the study of the disease of man, its diagnosis, and its cure.* The science of medicine should never take precedence and exclude the art. You have placed over the main entrance door of this Institution a quotation from an ancient Book of the Hebrews. The wisdom of Jesus, the son of

Sirach, or Ecclesiasticus,—may I quote  
it more completely

“Honour a physician with the honour  
due unto him

For the uses which you may have of  
him

For the Lord hath created him

For of the most High cometh healing,  
and he shall receive honour of the  
king

The skill of the physician shall lift up  
his head

And in the sight of great men he shall  
be in admiration

The Lord hath created medicines out  
of the earth,

And he that is wise will not abhor  
them

And he hath given men skill,

That he might be honoured in his  
marvellous works

And of his works there is no end,

And from him is peace over all the  
earth”

# Abstracts

*The Reactions of the Body to the Short Cold Bath* By W H RILEY, M D (Bull of the Battle Creek Sanitarium, August, 1928, p 129)

As a result of a thorough study of the effects of the short cold bath upon man Riley concludes that it increases the circulation and nutrition of the skin, increases muscle tone, increases muscular endurance and capacity, lessens muscular fatigue, increases the force, and lessens the rate of the heart beat, increases the tone and nutrition of the blood vessels, increases systolic and pulse blood pressure, decreases diastolic pressure, stimulates and improves the circulation, increases the depth and rate of respiration, increases the oxygenation of the blood, increases absorption of oxygen, increases the metabolism and chemical changes of the body, increases the production and elimination of  $\text{CO}_2$ , increases heat elimination and production, increases the number of blood elements and hemoglobin in the blood, improves the appetite, stimulates digestion, increases peristalsis of the digestive tract, helps to relieve constipation, increases the activities of the kidneys, increases the output of total fluid, solids and urea in the urine, increases the normal irritability and conductivity of the nerves, improves nerve tone, and is a general tonic. The short cold bath is very useful in all asthenic and neurasthenic states and in all chronic diseases where the different functions of the body are below normal. It is useful in various digestive troubles, constipation, different forms of anemia, and in cases where the circulation is below the normal. It is very valuable in improving vasomotor tone and the tone of the heart muscle and in cases of low blood pressure. There are many individuals who lead a sedentary life and who develop a weak heart muscle and a condition in which the muscle tone of the heart is greatly decreased. A short cold bath repeated daily is one of the

best heart tonics when properly used. In cases of severe diseases of the heart it should be used continuously and care should be taken that too cold applications are not made in cases in which the heart muscle is very weak. It is very valuable when the metabolic rate has dropped below the normal as in hypothyroid conditions, myxedema, and in all conditions in which metabolism and oxidation need to be stimulated. It is also valuable when properly used in cases of diabetes mellitus as it will aid in burning up the excessive amount of sugar in the blood. It is also useful in obesity and many other diseases. A great deal of skill may be shown in prescribing the short cold bath. It is important that the temperature and duration of the bath be suited to the needs of the patient. Too long an application or too large a dose of cold might do harm. The dosage of cold should be measured out by the physician with as much care as he would measure out a dose of medicine for his patient. The following cautions and contraindications should be observed. A short cold bath should never be taken when the body is cold. In this condition a warm bath is indicated rather than a cold one. It is usually a good plan to take a warm bath before taking a cold one, or at least to have the body warm. If the body is already warm, it may not be necessary. A short cold bath should never be taken when the body is tired, as it increases the activity of all the organs of the body and liberates energy. When one is tired his ability to react to the short cold bath is greatly lessened, and consequently he cannot get as much good from it as when he is rested. There are certain conditions and diseases of the body in which the short cold bath may be contraindicated or should be used very cautiously and in small doses. In conditions of shock and collapse the use of cold is contraindicated. During the two extremes of life, that is, in in-

fancy and old age, cold should be used very cautiously. In diseases of the kidneys the application of cold water to the body should be used very cautiously, and in advanced disease of the kidneys it is contraindicated. There is a very close relation between the kidneys and the skin, and in advanced diseases of the kidneys the application of cold to the surface of the body may greatly interfere with the function of the kidneys. In cardiovascular diseases and arteriosclerosis, particularly in the advanced stages of these conditions, cold should be used with caution and in small doses, also in high arterial hypertension. In patients suffering from an apoplectic stroke or in the hemiplegic state following apoplexy cold should be used in small doses and cautiously. In hyperthyroidism and in all conditions where the metabolic rate is above the normal, a short cold bath is contraindicated, as it increases the metabolic rate. In cases where cold should be used with caution and in small doses a short cold bath may often be used to good advantage in the form of a cold wet hand rub, cold mitten friction and cold wet towel rub, or some other similar mild application of cold. By these methods the tonic effect of the cold may be obtained without aggravating disturbing symptoms.

*Studies in Experimental Syphilis VIII*  
*On the Localization of Syphilitic Lesions in Inflamed Areas* By ALAN M. CHESNEY, M.D., THOMAS B. TURNER, M.D., and CHAS. R. HALLEY, M.D. (Bull. of the Johns Hopkins Hospital, 1928, XLII, pp. 319-334)

These workers present a series of experiments in which rabbits with either healed or granulating wounds (or both) upon their backs were subsequently inoculated intratesticularly or intravenously with a virulent strain of *Spirocheta pallida*. In each instance syphilitic lesions developed in the scars of the wounds. These lesions exhibited a marked tendency to conform to the pattern of the scars. The incubation period of the lesions developing after intravenous inoculation corresponded closely with that of lesions which develop at the site of inoculation after subcutaneous injection. From this it is inferred that shortly or immediately following intravenous inoculation the spirochetes reach

the scar and are deposited there. The histories of two patients are presented in whom syphilitic lesions developed in previously traumatized areas of the skin, when the syphilitic infection was acquired subsequent to the injury. It is concluded that recent non-specific inflammatory reactions of the skin of both rabbits and human beings, resulting from wounds, constitute foci favorable for the lodgement and growth of spirochetes coming from within the body, and predispose to the evolution of syphilitic lesions in those areas. These findings are in accord with old and well-known clinical evidence as to the predisposition of traumatic lesions in syphilitics to the development of gummatous lesions. Other experimental work by Chesney and associates has shown that granulation tissue in the rabbit appears to constitute a relatively unfavorable environment for the survival and growth of streptococci and staphylococci, whereas it appears to offer a favorable locus for the survival of the spirochetes of syphilis. This difference in behavior of granulation tissue in the rabbit to different kinds of pathogenic microorganisms makes it difficult, if not impossible, to formulate a general principle, applicable alike to all types of bacteria, regarding the susceptibility of granulating wounds to bacterial infection. The explanation of the difference in the reaction of granulating wounds towards syphilitic infection on the one hand, and towards streptococcal and staphylococcal infection on the other, is not by any means clear, and must be left for the future to determine. Factors other than mechanical must operate but what they are we do not know at the present time.

*Gastritis phlegmonosa (Magenphlegmone)*

By H. FINSTERER (Ergebn. d. Chir. u. Orthop., 1928, XXI, 543)

Three cases of this relatively rare form of gastric disease are reported in detail, and their pathogenesis and clinical features discussed. In diffuse phlegmon the submucosa shows the most severe changes, the entire stomach may be involved, or the infiltrating process may be confined to one portion of the organ, as the pyloric region. The latter form is to be differentiated from the so-called gastritis suppurativa abscedens in which there are one or



more sharply localized abscesses 78 per cent of the cases of phlegmonous gastritis have shown the presence of streptococci of high virulence. The patients usually die within 24-48 hours after the appearance of the acute symptoms. The affection is found almost exclusively in men of the laboring class, at about 40-50 years of age. The clinical symptoms consist of severe pains and distress in the upper abdomen, nausea and vomiting. The diagnosis is usually first made at the operation or autopsy. The prognosis is wholly bad in the diffuse form, in the circumscribed form surgical incision of the abscess and drainage may lead to recovery. Out of 17 cases in which resection was done 15 recovered. Among these cases were very severe ones with acute onset. It is probable that phlegmonous gastritis is of more frequent occurrence than it is now generally supposed to be.

*The Increased Mortality Rate of Cancer*

By H. E. EGGERS (The Jour. of Cancer Research, March, 1928, p. 9)

The increase in the reported mortality rate of malignant disease has attracted popular attention, and has been used as propaganda in various publications intended for the instruction of the laity in a knowledge of cancer and its possible prevention. If these statistics are to be taken at the face value of the figures themselves the death incidence for cancer has grown rapidly. It does not necessarily follow that any causes are operative in this increase other than the greater survival of a large portion of the population to an age at which their cancer susceptibility shows itself. From 1900 to 1917 there was a practically constant rate of increased mortality both for cancer and the degenerative diseases considered as a whole. Throughout this period the ratio of cancer deaths to those from the degenerative diseases remained almost the same, fluctuating around an average of 0.198. The individual degenerative diseases, while showing a fairly constant rate of increase, fluctuated more than did the group as a whole. With the occurrence of the influenza epidemic of 1918 all of the diseases peculiar to advanced age showed diminished death rates. This diminution was very transient for cancer, and apoplexy was somewhat longer continued for

organic heart disease, and was in 1924 still present almost to its original degree in the case of chronic nephritis. While the cancer death rate had resumed its interrupted normal trend by 1921, the degenerative disease ratio was still unduly low in 1924, due in great part to the reduction of deaths from chronic nephritis, and in smaller part to the reduction of deaths from diabetes. Aside from the exceptional course of the chronic nephritis death rate, cancer and the combined death rate from the other usual diseases of advanced age show an almost strictly proportionate rate of increase for the twenty-five year period. Unless there has been an actual relative decrease in cancer incidence in the period covered here, increased accuracy in diagnosis should have been reflected in an increase of cancer over that of the other diseases of similar age distribution, since cancer should in all probability be more frequently missed than erroneously diagnosed at present. There is no indication of such an increase during the twenty-five years of this report. If human mortality statistics are a poor thing—which undoubtedly they are—according to present indications they seem likely to remain so until the time of universal autopsies—and then their value will depend upon a very high standard of accuracy in the pathological diagnoses—also perhaps incapable of realization in this country under present conditions.

*Ringworm of the Hands and Feet* (United States Public Health Service, Bull. Sept. 18, 1928)

Recently it has been pointed out by Surgeon General H. S. Cumming, of the United States Public Health Service, that within the past few years throughout the whole United States many persons have been affected with an eruption of the hands and feet that is most marked during the hot weather. Information is slowly spreading among the public that in many instances this trouble is due to infection with a ringworm parasite. Medical knowledge of ringworm of the hands and feet is comparatively recent.

The disease is remarkably frequent, and it is probably that at least one-half of all adults suffer from it at some time. In the University of Pennsylvania a careful survey

of all students showed that over 60 per cent were affected with the ringworm organism. This work was definitely proven and not mere clinical diagnosis, for organisms were found in all cases. It is met with in every part of the country and is more frequent in the South than in the drier and colder climates.

It is said that in the Gulf States practically the entire population has had the disease at some period.

Almost everyone who uses a swimming pool, a golf club, an athletic club or any place where there is a common dressing room has the infection upon his feet. It is highly probable that the development of club life, the great increase in the number of swimming pools, and probably the general tendency of the American public to spend a certain amount of time in hotels, is largely responsible for the increase in this disease.

Ringworm of the hands and feet is caused by a vegetable parasite which is a distant cousin of the well-known mould that grows upon stale bread. In addition to living upon the human body it can probably live and grow elsewhere, and can resist drying for a long time. In fact, it is a remarkably resistant organism for it takes at least fifteen minutes of boiling to kill one. There are a number of varieties of ringworm parasite and it is highly probable that some are much more difficult to cure than are others. Unfortunately, at the present time, more exact knowledge on this point is needed.

Any type of person can be affected, whether well or ill. Food has nothing to do with the disease. Even the much talked of acidosis can hardly be credited to be the cause. The disease is much more prevalent during heated spells. Any occupation that entails long continued heating of the feet may be a predisposing cause or may aggravate an attack. Hot floors are bad. Feet should not be kept upon a radiator.

The disease is usually acquired by walking barefooted where the unshod have trod. Bath mats are justly blamed, and it is probably that ringworm can be acquired from them just as warts upon the soles of the feet can be. As already mentioned, common dressing rooms are probably the most frequent places where the disease is picked

up. However, it can also originate in hotels and from the use of infected towels or soap. There is no good proof that the water in swimming pools is in any way responsible.

In many instances either feet or hands alone are affected, but in the majority of instances traces of the condition can be found upon both. In its mildest form the disease exists as either a little cracking or a little scaling between the toes. In many instances the so-called soft corn is really due entirely to infection with ringworm parasites. Other common types of lesion are those in which there are either few or many blisters, a diffuse scaly eruption and, lastly, wart-like growths. Any portion of the hands or feet may show one of these eruptions. Rarely they may extend as high as the elbows or knees. When the blisters break, fluid always escapes to the surface and there is a wet oozing surface that usually becomes covered with scabs. Itching is frequently intense.

In a few cases a pus infection occurs and rarely abscesses may develop. These may be upon the hands or the feet or in the lymphatic glands which drain the involved areas. This is the condition sometimes known as "blood poisoning." Fortunately, it is rarely serious.

In many people the disease is by no means a mild one. Out of 161 consecutive cases it was found that 14 were totally disabled and 32 partially disabled. In some instances this disability lasted as long as three months.

In certain cases the body gains some resistance against ringworm organisms, just as it does against many other infectious diseases. However, one attack does not aid in guarding against subsequent ones. It should always be remembered that the ringworm organisms exist deep down in the skin, and this, of course, is the reason why they are so difficult to kill.

A few other conditions may resemble ringworm infection. Yeast may grow between the fingers or toes and give rise to lesions that closely resemble those caused by ringworm. The blisters of poison ivy may have a superficial resemblance. It is often alleged that poison ivy recurs each year upon the hands of some individuals, but in many instances the trouble is due to a ringworm infection. Many persons know that the hand-

ling of the house primrose plant is frequently followed by an eruption of blisters upon the fingers, and more rarely, the hands, wrists and even the feet. This condition too has been mistaken for ringworm. In fact, almost any type of chemical or mechanical irritation may be responsible for skin troubles that closely resemble those caused by ringworm.

The disease never invades the scalp, and it is excessively rare upon either the face or body. Almost all cases can be temporarily cleaned up, and apparently about 50 per cent can really be cured. Because of the great frequency of the disease it is difficult to tell whether a fresh outbreak is due to a recurrence or to a new infection.

An individual affected with ringworm should not use a bath mat. It is much wiser to step upon a section of newspaper and to burn that. Likewise the affected person should be most scrupulous about having his own towels and soap, and his socks, slippers and shoes should be worn by no one else. The use of light canvas slippers in dressing rooms would probably result in a marked decrease in the frequency of the disease. The floors of these dressing rooms should be washed and frequently treated with antiseptic solutions. A person in the active stage of ringworm should certainly sleep alone. Likewise, in the presence of lesions upon the hands, he should not dance, drive a car unless with gloves, hold to car straps or touch any object which others might also touch. It is possible that doorknobs may convey the infection much more frequently than we know.

There is no type of serum which has the slightest effect upon the condition. A person suffering from the disease should soak the affected parts in salt solution at least once a day. This, it will be remembered, is a common type of treatment for infections in all hospitals. Practically every known type of antiseptic has been employed but no one has met with universal commendation. Almost every physician has his own favorite method of treatment. Very light doses of the X-ray frequently exert a most beneficent influence, but they do not prevent the disease from returning. It has frequently been noted that those going to the seashore and

exposing themselves to the sun and salt water often recover in a short space of time. This observation has led to the use of ultra-violet light, and, under medical supervision, this remedy is often of great aid. Care must be taken that a marked burn is not produced. Of course, infected stockings, slippers or gloves must never be worn.

*Pellagra in Man and Black Tongue in Dogs found to be due to Similar Cause* (United States Public Health Service, Bull Oct 8, 1928)

The results of an important series of studies made by Dr Joseph Goldberger, and his associates, of the U S Public Health Service, have recently been published, which indicate that black tongue, a disease of dogs, and pellagra, a disease of man, are practically identical. In connection with such studies an interesting investigation has been made of the pellagra-preventing properties of sixteen foods. These foods are maize, wheat, wheat germ, cowpea, soy bean, milk, butter, cod liver oil, cottonseed oil, lean beef, pork liver, salmon, egg yolk, tomatoes, carrots and rutabagas.

It seems clearly indicated that so far as the studies have been conducted, the foodstuffs that appear to be good sources of the black-tongue preventive also appear to be good sources of the pellagra preventive, those that appear to be poor sources of, or lacking in, the blacktongue preventive likewise appear as poor sources of, or lacking in, the pellagra preventive. This, it should be noted, is not a mere similarity in distribution of the respective preventive essentials among the foodstuffs—it is a similarity in the potency of the action of these foodstuffs in the respective diseased conditions, and, thus, it would seem to constitute evidence of weight pointing to the identity of the preventive essentials, and, therefore, to the identity of blacktongue and pellagra.

The blacktongue-preventive potency of 16 foodstuffs has been studied and correlated to the pellagra preventive potency (or lack of it) of those, eleven in number, for which this was known, with the following results.

*Maize, if it contains any, is a poor source of the preventive for both blacktongue and pellagra.*

Whole *wheat* contains the blacktongue preventive, but in small amount

Commercial *wheat germ* contains, and may be rated as a relatively good source of, the preventive for both blacktongue and pellagra

The *cowpea* contains, but is a poor source of, the preventive for both blacktongue and pellagra

The *soy bean* contains the blacktongue preventive, but in relatively small amount, appreciably more, however, than the cowpea, but considerably less than the extracted wheat germ. So far as it goes the experience with the soy bean in the human disease is, at least, not inconsistent with that in the experimental disease of the dog

*Milk* contains the preventive for both the human and the canine disease, but contains it in relatively small amount

*Butter*, while not devoid of it, is a relatively very poor source of the blacktongue preventive, a conclusion that is in harmony with the experience with butter in pellagra

*Cod liver oil* would seem very poor in or lacking the preventive for both blacktongue and pellagra

*Cottonseed oil* contains little, if any, of the preventive for blacktongue. No specific study of the effectiveness of this oil in pellagra has been made, on the basis of general experience it seems unlikely that this oil contains the pellagra preventive in significant amounts

*Beef muscle* is a good source of the preventive for both blacktongue and pellagra

*Pork liver* is a good source of the blacktongue preventive, it has not yet been studied in pellagra

*Canned salmon* contains the blacktongue preventive. A study of its effectiveness in pellagra is in progress

*Egg yolk* contains the blacktongue preventive, specific study of its value in pellagra has not yet been undertaken

The canned *tomato* contains the preven-

tive for both blacktongue and pellagra but in relatively small amount

The *carrot* contains, but is a relatively poor source of, the preventive of blacktongue. Its reported failure in pellagra prevention is consistent with the indications of its feebleness as a blacktongue preventive

The *rutabaga* turnip contains, but is relatively poor source of, the blacktongue preventive. Its failure in pellagra prevention is consistent with its poverty in the blacktongue preventive

The pellagra-preventing vitamin is believed to be present in nearly, if not quite, all natural foods except the oils and fats, but in very greatly varying amounts. Thus there is very little in corn meal, white flour, or rice, somewhat more in wheat middlings, and a great deal in lean meat and powdered yeast. Unfortunately, it is not yet known just how much each food contains nor how much the body must have for the maintenance of health. In considering prevention and treatment it is, therefore, necessary to proceed on general principles, guided by such knowledge of relative values as we already have.

*Powdered yeast*—Dried pure yeast is the richest "P-P" (Pellagra Preventive) containing food at present known. It is also very rich in protein and in the beriberi-preventing vitamin, so that it should rate high as a food. This yeast is a microscopic plant cell used in baking and brewing. For use as a food the yeast plant should preferably be dead. In the home it may readily be killed by stirring the dry powder into some water and then boiling for about one minute. In the adult, 1 ounce a day (or two teaspoonsfuls three times a day) of the pure powdered yeast will of itself suffice to prevent pellagra. It may be taken in any way that is most convenient as, for example, in water, in milk, in tomato juice, in syrup or molasses

## Reviews

*The Treatment of Diabetes Mellitus* By ELLIOTT P. JOSLIN, M.D., M.A., Clinical Professor of Medicine, Harvard Medical School, Physician to New England Deaconess Hospital. New (4th) Edition, Enlarged, Revised and Rewritten. Octavo, 1006 pages, illustrated. Lea and Febiger, Philadelphia, 1928. Price in cloth, \$9.00, net.

Joslin's work on diabetes is the most important treatment of this subject available to readers in English, and is the most complete and logically arranged book on this subject to be found in any language. It is the only one that presents fully the modern view on diabetes and the diabetic, and the changed point of view is clearly and most ably revealed in the pages of this volume. It is larger by two hundred pages than the last edition, and has been largely rewritten and revised up to the last minute before publication. This, of course, makes a larger book, but it is so full of important and practical knowledge for the practitioner in the treatment of diabetes, that no single page even can be regarded as superfluous. The first three editions of Joslin's work met a great need and acquired at once a great reputation as being the most valuable guide to the treatment of diabetes ever presented to the medical profession. There has been no other book just like it, the author gave his own plan of treatment in the office, hospital and home, presenting the methods of treatment he has found to give the best results, and attempting to answer all the ques-

be severe or even moderately severe, but can usually be made mild. Into the present volume Joslin has put whatever of value he has seen, read or heard during the past five years that might be of value in the treatment of his diabetic patients. He has taken great pains to transcribe his own records in the belief that the accumulation of clinical facts is as important as the presentation of laboratory data. He has brought together from all sources information bearing upon the subject of treatment. Synthalin, myrtillin, the use of liver, the utilization of exercise, the cultivation of morale and advanced ideas upon diet, all are given full consideration. Since the diabetic child now constitutes a very definite problem for the practitioner, the section on diabetes in children has been much increased. The methods for the prevention of coma are given at length, because of the favorable results obtained through them. Arteriosclerosis is discussed in detail and methods of delaying its approach are suggested, while the delicate handling of the arteriosclerotic diabetic is fully described. The routine removal of infected feet, so dangerous for the diabetic, and the best methods of accomplishing this are indicated. In general, Joslin has sought to emphasize what hurts the diabetic and what helps him, and in each instance to tell how the one can be avoided and the other secured, as demonstrated in the care and treatment of his own patients. The complications of diabetes, once considered of minor importance, are now treated as being of major impor-

blood, respiration, diet, physiology, chemistry and pathology have been much enlarged, and much valuable matter added. Modern theories of diabetes are given adequate attention, and the present drift of thought on this disease shown. The greatest value of Joslin's work is found in its therapeutic and clinical discussions, it is weakest in its sections on etiology and pathology. From the former standpoint, the book is one that every practitioner should possess, or at least read, he will not find elsewhere such an assemblage of important facts bearing upon the care and treatment of the diabetic.

*Recent Advances in Diseases of Children*

By WILFRED J. PEARSON, D.S.O., M.C., D.M., F.R.C.P., Physician in Charge of Children's Department, University College Hospital, Physician to Out-patients' Hospital for Sick Children, Great Ormond Street, Physician to Cheyne Hospital for Children, Chelsea, Sometime Physician to Children's Department, Charing Cross Hospital, and W. G. WYLIE, M.D., M.R.C.P., Physician to Out-patients' Hospital for Sick Children, Great Ormond Street, Assistant Physician to Children's Department, Westminster Hospital, Assistant Physician to the Hospital for Epilepsy and Paralysis, Maida Vale. 593 pages, 18 plates and 32 figures. P. Blakiston's Sons and Company, Philadelphia, 1928. Price in cloth, \$3.50.

The authors have attempted to write a book on disease in children dealing with the subject primarily from the clinical standpoint, including such important recent additions to scientific knowledge as, in their view, have a bearing on the clinical study of disease in childhood. They have aimed at presenting the ailments of the young in the form and manner in which they are met in everyday practice, and to formulate principles for solving the problems of disease rather than merely to collect and record the work of others. This has necessitated statements of personal opinion and interpretation, they have expressed things as they see them, and have tried to prospect disease on simple lines, and to avoid being hidebound by conventional views. A survey of the material in the book shows that its title is a misno-

mer, there is more old stuff than new in its pages, and the material is not complete and is poorly arranged. It is of the manual type, and it is difficult to see just what useful purpose this volume plays as compared to any one of the better and more complete textbooks on children's diseases.

*Bronchial Asthma Its Diagnosis and Treatment*

By HARRY L. ALEXANDER, A.B., M.D., Associate Professor of Medicine in the Washington University Medical School, St. Louis, Mo., Associate Physician to the Barnes Hospital, St. Louis, Mo. 171 pages. Lea and Febiger, Philadelphia, 1928. Price in cloth, \$3.00.

During the last decade there has been aroused a greatly increased interest in asthma due to the discovery that bronchial asthma is an expression of human hypersensitiveness. The emphasis on the phase of the subject has tended to obscure other important studies that had been previously made. The purpose of the present book is to present an outline of bronchial asthma as a clinical expression of a constitutional defect and not as a disease entity. There are eight chapters and an appendix. These, in succession, deal with The Historical Considerations and Definition of Bronchial Asthma, Anatomical Considerations, Pathogenesis of Bronchial Asthma, Pathological Findings in Bronchial Asthma, Immunological Aspects of Bronchial Asthma, Clinical Aspects of Bronchial Asthma, Complications and Prognosis, Treatment and Diagnostic methods. The chapter on treatment deals at length with the modern methods of therapy, the book aiming at completeness of detail in regard to this phase of the subject alone. References are very fully given at the end of the chapters. This little volume constitutes a valuable monograph on this subject and contains most of the known facts concerning the phenomenon of asthma. Since this clinical entity is so frequently seen in general practice, the information given here will be very helpful to the general practitioner and internist.

*Diabetic Manual for Patients* By Dr. HENRY J. JOHN, M.A., F.A.C.P., Director of the Diabetic Department and Labora-

tories of the Cleveland Clinic 202 pages, 42 illustrations The C V Mosby Company, St Louis, Mo., 1928 Price in cloth, \$2 50

This manual has been written for the diabetic patient in the hope that it will aid him in successfully combatting his disease. It contains a simple explanation of the underlying causes of diabetes and gives careful, explicit directions for its treatment, which, while warning him of his constant need for medical supervision, will nevertheless make the diabetic confident of his own ability to care for himself and to lead a comfortable normal life. There are eighteen chapters entitled respectively: Introduction, What is Diabetes, The Role of Food in the Causation of Diabetes, The Relation of Obesity to Diabetes, Blood Sugar, Urine Sugar, Treatment of Diabetes Before the Discovery of Insulin, Treatment of Diabetes Since the Discovery of Insulin, Is there any Cure for Diabetes, Diabetes in Children, Diabetes in Persons of Advanced Years, Diabetic Arithmetic, Food Tables, Rôle of Insulin in the Treatment of Diabetes, Insulin Reactions, Acidosis and Coma, Hygiene for the Diabetic Patient and The Physician and the Patient. Following these there are two Appendices, one on Food Charts and one on Sample Menus. These chapters are written in a clear and concise style and embody the most important facts and considerations on diabetes that should be known to every diabetic. It is absolutely necessary for the latter to know the facts and to understand the nature of the disease and the principles of its treatment, if he is to cooperate successfully with his physician in the treatment, and without such cooperation the treatment will be a failure. This little volume offers to the layman just what he should know on his side in coping with the problem of treatment, and will be of great service to every diabetic who uses it.

*Recent Advances in Physiology* By C LORATT EVANS, D Sc (Lond.), M R C S, L R C P, F R S, Jodrell Professor of Physiology, University College, London Third Edition 403 pages, 86 illustrations P Blakiston's Son and Company, Philadelphia, 1928 Price in cloth, \$3 50

This is a new revised edition of what the author has called an Elementary Textbook of Advanced Physiology. Its aim has been to present to the student who has worked through the ordinary textbook an account of some of the problems with which physiologists have been concerned in recent years, and thus to serve not only to enrich the student's knowledge as regards subjects of contemporary interest, but also to form a convenient bridge by which he may, if he feels so disposed, pass more easily into the original literature of these subjects. Two new chapters on "Excitability and Chronaxie" and "The Nervous Impulse" have been added to this edition, and three chapters have been omitted. All of the remaining chapters have been considerably revised. Much of the new material is based upon articles in the *Physiological Reviews*, and the literature reviewed is indexed at the end of each section. The subjects discussed, in addition to those mentioned above, are: The Mechanism of Tissue Oxidations, Chemistry of Muscular Contractions, Physical Aspects of the Physiology of Muscular Contraction, Application of these Researches to the Physiology of Muscular Exercise in Man, Mechanism of Postural Reflexes and the Function of the Labyrinth, Conditional Reflexes, The Active Principle of Some Endocrine Organs, Thyroxin, Pituitary Principle, Insulin-Parathyroid, Origin of Blood Cells and Their Relation to the Connective Tissues, Carriage of Carbon Dioxide by the Blood, Reaction of the Blood and the Capillary Circulation. These sections are more or less elaborate abstracts of some of the important articles embodying physiologic research during the last several years. They are in part illustrated by reproductions of the original figures given in these articles. The book is, therefore, of convenience in presenting such a group of well-abstracted recent investigations in physiology, and the teacher and student in physiology will find the volume a time-saver in this respect.

*Laboratory Manual of the Massachusetts General Hospital* By ROY R WHIFFLER, M D, and F T HUNTER, M D, Second Edition, Enlarged and Thoroughly Revised 101 pages Lea and Fabiger, Philadelphia, 1928 Price in Cloth, \$1 75

The first edition of this work, published by the Massachusetts General Hospital in 1922, was prepared by a group of medical internes. Intended originally as a pocket outline of the routine laboratory work done by internes in the hospital, and for their guidance, it was soon found to be of interest to a much wider group, students and practitioners. A limited printing was therefore soon exhausted and a second edition undertaken. The original text has been carefully checked and in many instances revised by Drs Wheeler and Hunter. Certain procedures no longer used have been omitted. New laboratory tests such as the Rosenthal liver function test and the Van den Bergh test have been included. The greater portion of the chapters on Therapeutic technique and prophylactic measures is new. The procedures described are those actually in use today in the Massachusetts General Hospital and are sanctioned by its staff as those which daily experience has shown to be best suited for their intended purpose. There are six chapters entitled Laboratory Work Indicated, Examination of Specimens, Collection of Specimens, Special Diagnostic Procedures, Therapeutic Technique and Prophylactic Measures. These are followed by an Appendix and Index. This is a very practical and useful laboratory manual for the medical student and interne. The methods are well-chosen, they are clearly and concisely described, and the small size and limp binding make it a very convenient volume for the pocket.

*Criteria for the Classification and Diagnosis of Heart Disease*. By a Committee, JOSEPH H BAINTON, M D, ROBERT L LEVY, M D, W C MUNLY, M D, M C, U S A, HAROLD E B PARDEE, M D, Chairman. Appointed by the Heart Committee of the New York Tuberculosis and Health Association, Inc. Arranged in Conformity with the Nomenclature for Cardiac Diagnosis Approved by the American Heart Association. 92 pages. Paul B Hoeber, Inc., New York, 1928. Price in cloth, \$1.50.

Uniformity of nomenclature and uniform criteria for using the nomenclature are necessary for the effective study of any disease,

in order that observers in different places may know that they are using the same terms for the same conditions. Such labels, or nomenclature, should as far as possible be descriptive and descriptive only of the conditions which they indicate. The criteria should be precise definitions of the states named in the nomenclature. In 1923 the Committee on Cardiac Clinics of the New York Heart Association prepared a nomenclature covering diseases of the heart and blood vessels, which it adopted, and later, with certain changes, was adopted by the American Heart Association and has been used with success in all parts of the country. It became obvious that after the completion of the nomenclature the next need was the establishment of definite criteria for diagnosis. A committee was appointed for this purpose, and after a careful consideration extending over two years produced this book, which has been approved and adopted by the Heart Committee. It is hoped that these criteria proposed by experts will prove to be an extremely practical guide for correct diagnosis and hence for proper management and treatment, and that this book may serve as a manual for the practicing physician and of great aid in diagnosis. The Heart Committee realizes that thoughtful use of the criteria will undoubtedly suggest modifications and hopes that all who use the book will not hesitate to send criticisms and suggestions for its improvement. After all, any committee of this kind, can only use the data available at the given time of compilation, and the difficulty with criteria of this kind is that they very soon fall behind the actual knowledge of the time. Criteria must be categorical and brief, omissions, therefore, are bound to occur. On page 23, under Toxic, the toxic action of diphtheria upon the heart is mentioned, but not that of typhoid fever, in severe cases of which myocardial lesions comparable in severity to those of diphtheria are common and very important clinically. Typhoid fever is apparently not mentioned in the book as a factor in the production of cardiac disease. The anatomical criteria given are inadequate in some instances, as, for example, under Acute Myocarditis, on page 40, which is both inadequate and inaccurate, in that it em-



phasizes only the rheumatic form. Under adherent pericardium surely the clinical and anatomical syndrome of Pick's disease should have been mentioned, as this is usually the only clinical foundation for a diagnosis of synechia cordis. Why also, should not this term have been included in the nomenclature and criteria? The physical signs of aortic syphilis are not up to date. The criteria of

congenital abnormalities are very inadequate from the diagnostic standpoint, and consultation with Maude Abbott's Monograph is advised. The reviewer realizes the impossibility of completeness in a categorical list of criteria, but if these are to be used as a manual for diagnosis, a greater perfection of completeness in the most essential diagnostic data must be attained than is shown here.

# College News Notes

## OBITUARY

Dr Henry Green Brainerd, Los Angeles, California, (Fellow, April 3, 1922) Died July 23, 1928, age, 76 years

Dr Brainerd received his Bachelor of Arts Degree from Dartmouth College and his Degree of Doctor of Medicine from the Rush Medical College in 1827. He did postgraduate study at Bellevue Hospital Medical College, of New York, New York Postgraduate Medical School and Hospital and in London. He was Assistant Superintendent of the Iowa Hospital for Insane from 1878-86, Superintendent of the Los Angeles General Hospital from 1882-92, Professor of Mental and Nervous Diseases at the University of Southern California College of Medicine at Los Angeles from 1887-1911 and Dean of the Faculty of Medicine of the same institution from 1889 to 1902. He was Consultant to the California Lutheran and St Vincent's Hospitals from 1910 to the date of his death, and Consultant to the Methodist and Hollywood Hospitals since 1920. He was chairman of the Draft Board during the war.

Dr Brainerd was one of the most capable and best beloved physicians in Los Angeles. He always gave his time and strength for the betterment of medicine, and he was the first Neurologist in Los Angeles. Dr Brainerd was President of the University Club, twice President of the California Med-

ical Association, and had been President of all the local medical organizations.

About three hundred physicians gave him a testimonial dinner on May 23d, in honor of his seventy-sixth birthday. He has been an active Fellow of The College since 1922 and offered valuable suggestions and help on many occasions.

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Dr Ralph H. Hunt, East Orange, New Jersey,, (Fellow, February 24, 1926), died July 9, 1928, of carcinoma of the intestine,, aged 59.

Dr Hunt received his Bachelor of Arts and Master of Arts from Bowdoin College, and graduated from the Medical School of the same institution in 1894. He was a member of the Psi Upsilon and the Phi Beta Kappa fraternities.

From 1896-99, Dr Hunt was Assistant Surgeon to the National Soldiers Home at Togus, Maine, from 1894-95, he was House Surgeon at Maine General Hospital, from 1899-1900, he was a member of the staff of the Mothers' and Babies' Hospital of New York. His more recent appointments were—Chief of the Tuberculosis Clinic at the Orange Memorial Hospital Outpatient Department 1905 to date, Attending Physician Orange Memorial Hospital 1910 to date, Chairman Advisory Board, Essex County Tuberculosis Sanatorium 1922 to date.

During the War, Dr Hunt was Captain in the Medical Officers Training Corps and later Lieutenant Colonel in the Medical Corps of the U S Army, American Expeditionary Forces

Dr Hunt was ex-President of his local county medical society, a member of the Maine State Medical Society, of the American Medical Association, of the American Public Health Association and of the National Tuberculosis Association. Dr Hunt was known as one of the leading internists of New Jersey, actively engaged in hospital and educational medical work. His standing in the community, both as a citizen and as a physician, was of the highest possible order.

Dr George E Brown (Fellow), Rochester, Minn, recently addressed the Region Medical Society on "Essential Hypertension."

Dr Louise Taylor Jones (Fellow), Washington, D C, was elected President of the Medical Women's National Association at Minneapolis during June.

Dr John A Toomey (Fellow), Cleveland, Ohio, has been promoted to Assistant Professor of Pediatrics for three years at Western Reserve University School of Medicine.

Dr Wm C Rucker (Fellow), in command of the U S Naval Hospital No 14, at New Orleans, and Dr Wm M Simpson (Fellow), Dayton, Ohio, Pathologist to the Miami Valley Hospital at Dayton, appeared on the program to lead discussions at the annual meeting of the Medical Society of Wisconsin at Milwaukee on September 12-14.

Dr Frederick J Epplen (Fellow), Seattle, Wash, was elected Secretary of the

Pacific Northwestern Medical Association at its seventh annual meeting in Tacoma, July 5-7.

Dr William Engelbach (Fellow), St Louis, conducted a clinic on July 19 before the Twin Lakes District Medical Society at Twin Lakes, Iowa.

It was recently announced that Dr Engelbach after more than twenty years practice in St Louis, will take a leave of absence for a year or more to write a system on Internal Secretions. For many years Dr Engelbach was Professor of Medicine at St Louis School of Medicine and Chief of Staff at the St Johns Hospital. He is now a member of the staff of the City Hospital, Missouri Baptist Sanatorium, the Maternity Hospital and the new Jewish Hospital. He is a former President of the American Association for the Study of Internal Secretions and of the St. Louis Medical Society.

Dr John H Musser (Fellow), New Orleans, La, addressed the Homochitto Valley Medical Society at Natchez, Miss, July 12 on "Euphyllin."

Dr Ray M Balyeat (Fellow), Oklahoma City, Okla, addressed the Southeastern Oklahoma Medical Association at McAlester, June 20, on "Diagnosis of Pulmonary Tuberculosis."

Dr Wm C Cheney (Fellow), Memphis, Tenn, addressed the Memphis and Shelby County Medical Society, July 5 on "Diagnosis and Treatment of Cirrhosis of the Liver."

Dr Oliver T Osborne (Fellow), Professor of Therapeutics, Emeritus, Yale School of Medicine, New Haven, Conn, and a member of the Board of Governors of The College representing Connecticut, has just issued through the American Medical Association the eighth edition of his book, "Handbook of Therapy."

Dr M L Turner (Fellow), Berwyn,

Maryland, has from time to time contributed valuable collections to the new library of The American College of Physicians. Dr Turner's keen interest in this movement has lead to several other contributions. In a recent letter addressed to The College, Dr Turner wrote, "Personally, I think The College should have a general library, part exclusively the writings of Fellows and the remainder consisting of books by general writers. As every Fellow has a library, many of which were started before The College, the above arrangement would encourage him to will his medical books to this College." Such a plan of procedure would not only build up a valuable library in The American College of Physicians but provide a memorial to the member and create a useful purpose for his books.

Dr William R Bathurst (Fellow), and Dr Oliver C Melson (Fellow), both of Little Rock, Ark, and Dr Henry Rudner (Fellow) of Memphis, Tenn, recently addressed the First Councilor District and Northeast Medical Society at its meeting at Jonesboro, Ark.

Dr Williams Engelbach (Fellow), St Louis and Dr Isadore D Bronfin (Fellow), Denver, addressed the fifty-eighth annual meeting of the Colorado State Medical Society at Colorado Springs, September 11-13, on "Endocrine Disorders, Diagnostic Clinic," and "Diagnosis of Tracheobronchial Tuberculosis in Childhood," respectively.

Dr Rudolph W Arndt (Fellow), Denver, is one of a group who conducted a symposium on pyelitis in connection with the same meeting.

Dr Grant H Laing (Associate), Chicago, has been promoted to Assistant Clinical Professor, Department of Medicine, Rush Medical College, as of July 1, 1928.

Dr Edwin W Gehring (Fellow), Portland, Maine, read a paper on John and Wm Hunter before the meeting of the York County Medical Society at Dunstan, Maine, July 12.

Dr Edward L Tuchy (Fellow), Duluth, and Dr Henry L Ulrich (Fellow), Minneapolis, assisted in the conduct of a heart symposium before the Annual Meeting of the Northern Minnesota Medical Association at Fergus Falls on August 20 and 21.

Dr Edward J G Beardsley (Fellow), Philadelphia, delivered the address at the graduating exercises of the Interne Staff of the Philadelphia General Hospital on June 26.

Major General M W Ireland (Fellow), Surgeon General of the U S Army, recently received decorations awarded during the World War. A considerable number of medals, diplomas and decorations bestowed by foreign government on army officers during the World War, and even previous thereto, were not distributed at the time because army officers heretofore have been prevented from receiving any decoration from foreign countries. By authority of an act of Congress, approved in May, these accumulated decorations have now been distributed.

Dr Howard S Brasted (Fellow), Hornell, New York, has recently been appointed to the Consulting Staff of the Steuben Sanitarium, an old and well established institution with a record of forty years in the treatment of medical and nervous cases. Dr Brasted's father held a similar position during his lifetime.

Dr William L Holman (Fellow), Toronto, was recently appointed professor of bacteriology and associate director of applied bacteriology on the faculty of medicine of the University of Toronto.

Dr George H Whipple (Fellow), Rochester, N Y, was appointed Chairman of the Committee on Visual and Motion Picture Education at the meeting of the meeting of the Board of Trustees of the American Medical Association at Chicago, September 7.

At the meeting of the Fourth Councilor District Medical Society of Wisconsin at Lancaster, Wis., August 6, Dr. Rock Sleyster (Fellow), Wauwatosa, spoke on "Psychoneuroses and Mental Disorders" and Dr. Ray C. Blankinship (Fellow), Madison, spoke on "Constipation."

Dr. Charles W. Stone (Fellow), Cleveland, President of the Ohio State Medical Association, addressed the Fifth District meeting of that society at Cleveland, September 21. Dr. Clyde L. Cummer (Fellow), Cleveland, was in charge of the general arrangements for the meeting.

Dr. J. B. McElroy (Fellow), Memphis, addressed the meeting of the Montgomery County Medical Society at Dunbar Cave, Tenn., on August 16.

Dr. Noble Wiley Jones (Fellow), Portland, Oregon, conducted a medical clinic on June 7 at the general hospital at Pocatello, Idaho, where the Pocatello County Medical Society acted as host to a large number of physicians of southeastern Idaho.

Dr. Lewis B. McBrayer (Fellow), Southern Pines, N. C., is a member of the committee administering the funds of the North Carolina Medical Foundation, created by the Medical Society of the State of North Carolina. "The purpose of the foundation is to encourage gifts for charitable purposes connected with the activities of the medical society." It is understood that this fund shall be available for "the promotion of medical science, the encouragement of postgraduate medical instruction, the correlation of medical activities, the education of the public about medical matters, the helping of indigent physicians and their families, and for any other object that may reasonably be construed as promoting medical science and practice in the state."

Dr. Walter M. Simpson (Fellow), Dayton, Ohio, delivered a lecture under the auspices of the Mayo Foundation at Rochester, Minnesota, June 22, entitled "Experi-

ences with Fifty-three Cases of Tularemia Occurring in Dayton."

On June 6, Bucknell University conferred the honorary degree of Doctor of Science at its commencement on Dr. S. Calvin Smith (Fellow), Philadelphia, Pa.

Dr. William S. Thayer, Baltimore, Dr. Julius H. Hess, Chicago, and Dr. Stuart Pritchard, Battle Creek, are Fellows of The College who were invited speakers at the joint annual meeting of the Idaho, Montana and Wyoming State Medical Associations at the Canyon Hotel in Yellowstone National Park, August 27-29.

Dr. A. S. Warthin, Editor of the Annals, spent the month of August in the Hawaiian Islands. At a special meeting of the Honolulu Medical Society he gave an address on the Pathology of Latent Syphilis. Cooperation was also secured with Drs. Arnold, Fennell and Larsen, of Honolulu, for the carrying-on of an investigation of latent syphilis in the native and Oriental races of the Island, in connection with the investigations on latent syphilis to be carried out under a grant from the National Committee on Syphilis at the Pathological Laboratory at the University of Michigan.

Dr. Russell C. Pigford (Associate) has resigned his post as full-time instructor in the Department of Medicine of Tulane University, New Orleans, to engage in private practice in Tulsa, Oklahoma.

Dr. Lea A. Riely (Fellow) and family of the clinics of France. Dr. Riely is professor of medicine at the University of Oklahoma Medical School. He reports that the Medical Department of the University of Oklahoma has heretofore functioned as two separate units, the first and second years with the University at Norman, Okla., and the second and third years at Oklahoma City. In September the Medical Department will open in a newly erected building in Oklahoma City with the University Hos-

pital and the Crippled Children's Hospital as teaching hospitals

Dr H Sheridan Baketel (Fellow), Jersey City, N J, and Professor of Preventive Medicine and Hygiene in the Long Island College Hospital, Brooklyn, was re-elected President of the Medical Alumni Association of Dartmouth College at the time of the last Commencement. He has occupied this position since 1923

Dr C S Danzer (Fellow), Brooklyn, N Y, delivered an address on "Cardio-Vascular-Renal Diseases from an Insurance Standpoint" at the convention of Medical Examiners of the Judea Life Insurance Company on September 9 at the Waldorf Astoria Hotel, New York City. Dr Danzer is also scheduled to read a paper on "Certain Constitutional Factors in Peptic Ulcer" before the section on Gastro-Enterology of the Southern Medical Association in Asheville, N C, November 14.

Under the Presidency of Dr Arthur C Morgan (Fellow), Philadelphia, the Pennsylvania State Medical Society held its seventy-eighth annual meeting at Allentown, Pa, October 1-4.

Dr William S Thayer (Fellow), Baltimore, President of the American Medical Association, and Dr Henry A Christian (Fellow), Boston, delivered addresses at the meeting

Dr George E Pfahler (Fellow), Philadelphia, representing the American Roentgen Ray Society, Dr Edwin C Ernst (Fellow), St. Louis, representing the Radiological Society of North America, Dr B H Orndoff (Fellow), Chicago, representing the American College of Radiology, and Dr Albert Soland (Fellow), Los Angeles, representing the American Radium Society, were official delegates from the United States to the International Radiological Congress at Stockholm, Sweden, during August.

Dr Charles H Neilson (Fellow), St Louis, has been appointed Associate Dean of the St Louis University School of Medi-

cine to succeed the late Dr Don R. Joseph. Dr Neilson is President of the St. Louis Medical Society, a graduate of the Rush Medical College, and for a number of years has been a member of the staff of the Medical School of which he now becomes Associate Dean

Under the Presidency of Dr Herman N Bundesen (Fellow), Chicago, the American Public Health Association held its fifty-seventh annual meeting in Chicago, October 15-19. The American Social Hygiene Association and the American Child Health Association held their meeting jointly with the American Public Health Association

#### DIRECTORY OF NEW MEMBERS

Mr E R Loveland, Executive Secretary of The College, 133-135 S 36th Street, Philadelphia, Pa, announced the completion and distribution of the new SUPPLEMENT TO THE 1927-28 YEAR BOOK OF The American College of Physicians on September 10. A considerable part of the summer months were spent by Mr Loveland and his staff in preparing this directory of new members to supplement the 1927-28 Year Book that was published during the summer of 1927. The complete Year Book is printed every second year, and a Supplement is published during the intervening year.

This Supplement contains the names and biographical detail of two hundred and eighty-eight new members, two hundred and thirty-seven Fellows and fifty-one Associates. It also contains names of present officers and personnel of the various Boards and Committees, list of deceased members, resignations accepted, list of medical schools of the United States and Canada, college, professional and honorary fraternities. The same policy with regard to the type of biographical detail is used in this Supplement as used in the last Year Book. Before the publication of the next regular edition of the Year Book, the Committee will duly consider several recommendations now on file for revision of the character and scope

of information published. Naturally, it was impossible in this Supplement to make corrections or additions to biographical data printed in the 1927-28 Year Book proper.

An examination of the new elections will disclose that from July 1, 1927, to July 1, 1928, The College has had a most successful and commendable growth. Officers and members of the Board of Regents and the Board of Governors have worked earnestly, enthusiastically, and with a vision of the

responsibilities of The College as "the one national organization that offers useful service to all Internists and to the general cause of Internal Medicine."

Any one desiring to secure a copy of the Supplement may send an order with enclosure for Fifty Cents to the Executive Secretary. Complimentary copies were distributed only to paying members in good standing.

# Angina Pectoris\*

## A Clinical Analysis of 200 Cases

By MORRIS H. KAHN, M. A., M. D., AND JOSEPH BARSKY, M. D.,  
*New York City*

THE following study is based upon a critical analysis of 200 cases of angina pectoris that have been carefully observed and studied over a period of a few years. We shall endeavor, therefore, to support our assertions and impressions by the clinical material at our disposal rather than by opinions or extracts from the literature.

### TERMINOLOGY

The term "angina pectoris" calls to mind a condition in which pain in the chest occurs in attacks, radiating frequently down the left arm and associated with aortic and coronary disease. The pain is substernal rather than submammary, and arrests the patient in whatever he may be doing. He becomes conscious of a sense of oppression or constriction which may reach a high grade of intensity, and even a condition of intolerable anguish. There are, in addition, characteristic associated symptoms—notably a sense of impending death, accompanied by varying vasomotor disorders—cold sweat and deathly pallor. It could thus seem that the clinical

syndrome of angina pectoris is hardly to be mistaken. Yet the condition has a borderline of symptoms in which the picture is not so typical. These present themselves in two forms—one, in the form of what has been called "angina minor," and the other in prodromal symptoms.

Angina minor is used by us to indicate rather a transient attack of anginal pain of moderate or mitigated severity. We believe this application of the term is justifiable, although Osler applied the term to an undifferentiated group of neurotic, toxic, and vasomotor conditions in which some anterior thoracic pain was a symptom, and in which there were no signs of cardiovascular disease (1). From our present knowledge of the subject, we would dismiss the latter as a rather vague usage of the term, and employ it in the sense of mild angina pectoris.

We want to dismiss as indefensible the name "pseudo-angina pectoris" from the cardiologic nomenclature. This term particularly has no meaning. If it is applied to neurotic complaints without any organic basis, such complaints should receive their proper name. If, on the contrary, the diagnosis is not absolute, but left pec-

\*From the Dept. of Cardiovascular Diseases, Beth Israel Hospital, New York City.



toral or sternal pain is present, again the proper qualification should be made

#### PRODROMAL SYMPTOMS

The other group presents various prodromal symptoms which, in our observation, have eventually led up to typical attacks of angina pectoris (2). These cases are specially important and to be emphasized as they are quite common and stand the risk of being passed over as of little moment. The symptoms are often not recognized as anginal and their ominous significance is overlooked. This is particularly so because on physical examination no conspicuous cardiac signs are evident. The diagnosis in these cases must therefore be made on the subjective manifestations mainly. Altogether 83 of our 200 cases gave prodromal symptoms.

Mild prodromal attacks of angina pectoris often occur before typical attacks. The most characteristic symptom which persists often over a long period, and is as distinct evidence of the pathologic process going on behind the sternum as the anginal attack itself, is what the patients described as a "burning sensation" or a "burning pain" behind the sternum. This may be constant in the sternal region or may spread over the precordium and even to the back. Sometimes it is brought on by exertion, sometimes only by bending over, without any radiation and without any particular reference, otherwise, to the heart. A steady manubrial pain over a long period of time, or a continuous burning sensation should, therefore, be a warning signal in questionable cases.

It is important to remember this symptom as part of the picture of angina pectoris. In some cases the pain is located in the epigastrium and focuses attention to the stomach. Altogether, the distress, burning, or pressing across the front of the chest, "heart-burn," or precordial pain occurred in 40 cases as a prodromal symptom of angina pectoris.

In 32 cases, for a more or less prolonged prodromal period there was noted a degree of limitation of function, usually only mild, with shortness of breath on exertion and palpitation at times. Fatigue on exertion was noted by four patients. Attacks of unconsciousness occurred in four of the 20 cases. Paroxysmal tachycardia occurred in two cases before the anginal attacks developed, and also in one case presenting signs of mitral stenosis.

These indicate that the cardiac process preceding attacks of angina pectoris is a prolonged process and that the appearance of angina pectoris is a manifestation of an already more or less developed pathology in the aorta and coronary arteries.

#### TENDER SPOTS ON THE CHEST WALL

The particular emphasis brought out by these prodromal symptoms is to indicate the nerve mechanism by which pain is produced from the aorta-coronary artery area. It is well known that impulses passing to the cord from a diseased viscus produces a disturbance in the peripheral segment to which they pass, so that any stimulus applied to the area connected by sensory nerves with the segment will give rise to exaggerated sensations. This

hyperesthesia in angina pectoris is most commonly experienced over the upper intercostal regions and the sternum, but it may be ascertained to be present over part of the neck and arm as well

Tenderness may be discovered by the application of varying degrees of pressure with a blunt or with a sharp instrument, or by gently pinching the skin with the finger and thumb. We have endeavored to use uniform pressure by means of the thumb or the tip of the finger over the sternum and the ribs on each side, to elicit hyperesthesia or tenderness. Suddenly, the patient will assert a degree of tenderness over a certain point. This can be recorded, as we have done, by a circle painted with tincture of iodine. Several spots may thus be elicited and the chest then photographed for future reference (3).

Of the 200 cases examined, in 65 tender spots on the chest wall were unmistakably present. These often persisted continuously and increased following an attack. They were present in the right pectoral region in 33 cases, left pectoral region 24, precordial 39, sternal 7, epigastric 6, left interscapular 2, right interscapular 2.

#### CAUSE OF ATTACK

Whether the pain has its origin in the aorta or in the heart, it is generally accepted that it is primarily determined by vascular disease—i. e., by disease affecting the base of the aorta or the coronary arteries. Although innumerable theories have been advanced to explain the occurrence of angina pectoris, the immediate cause of these attacks is still unestablished.

Whether the attack follows only increased pressure in the aorta with tension exerted upon the adventitia, as Allbutt insists (4), or whether the pain results from extreme tension of the ventricular muscular walls as Mackenzie asserts (5), or whether it is due to a cramp of the heart muscle as Heberden who first described the condition believed (6), or of the coronary artery producing transient ischemia of the heart muscle (7), it is difficult in any particular case to decide.

Still another, though infrequent cause, for the onset of angina pectoris must be mentioned. We refer to the condition known as "heart strain" with symptoms of angina pectoris immediately following (8). By "heart strain" is meant an organic condition associated with the sudden development of symptoms referable to the heart and aorta which can be attributed to some unusual muscular effort or overexertion, and which result in physical disability of varying degree and duration.

With the varying pathological conditions that exist in each case, each of these may be the one explanation applicable in any particular case. In general, the causes may be classified on a theoretical basis as follows:

#### A Cardiodynamic causes

- 1 Tension of the ventricular walls (Mackenzie)
- 2 Cramp of the heart muscle (Heberden)

#### B Vascular causes

- 1 Tension of the adventitia of the aorta (Allbutt)
- 2 Intra-aortic pressure changes

3 Spasm of the coronary artery

4 Coronary occlusion

#### C Mechanical causes

1 Interference by gastric distention and high diaphragm

2 Reflex effects from subdiaphragmatic viscera

3 Postural and respiratory effects

#### D Toxic causes producing any of the above effects

1 Tobacco

2 Coffee

3 Toxic pressor substances in the blood

#### E Heart strain and the effects of exertion

### AGE AND SEX

But there are certain etiologic factors which deserve more particular consideration. The age of onset in the group of 200 cases studied is shown in Table I. Almost 22% of

TABLE I—AGE AND SEX INCIDENCE

Age	Males	Females	Total	Percent
30-40	35	8	43	21.5
41-50	62	16	78	39.0
51-60	38	17	55	27.5
61-70	16	6	22	11.0
71-80	0	2	2	1.0

the cases with angina pectoris had their first typical attack before the age of 40. It is important to recognize this fact, and not to dismiss as insignificant complaints of pain referable to the heart in young individuals. The largest number of cases began in the fifth decade in men, and in the sixth decade in women. Above the age of 60 years, the onset of angina pectoris was infrequent. The reason

for this may be that a first attack occurring later in life is sooner fatal.

There is a discrepancy in the age fractions between the grouping of cases of coronary sclerosis as found by autopsy and those of angina pectoris, indicating that in a certain number of cases the anginal picture may be due to disease of the aorta alone, and that many cases of coronary sclerosis will not have any symptoms of angina pectoris. Thus, in an analysis of 86 cases of coronary sclerosis proven by autopsy, Willius and Brown found that only 30 cases (34%) had had attacks of angina pectoris (9). In their series of coronary cases, the largest number occurred in the eighth decade.

It is well known that males are more likely to develop angina pectoris than females, and in our group the number was 151 males and 49 females. In previous reports in the literature the proportion of females is even smaller than in the series recorded here. The cause of this difference of sexual susceptibility lies mainly in the greater protection in women of the thoracic aorta from physical strain. On the other hand, all the women in our series did have severe and sudden stresses in their life as a causative factor.

### INFECTIOUS AND TOXIC CAUSES

It would seem that the acute infectious poisons such as those of rheumatism and other infectious diseases deserve recognition as important causes initiating vascular changes in the aorta and coronary artery area in early middle age (10). This is

evidenced in our table in which 79 out of the total 200 cases gave a history of recurring tonsillitis, and in 11 a positive history of acute articular rheumatism with fever was obtained. Fifty-seven of the cases gave a history of rheumatic pains as a conspicuous complaint. As a direct cause of angina pectoris, therefore, we believe with Allbutt that rheumatism has not been sufficiently emphasized. Recent research has indicated that the rheumatic poison leaves its effects on the various tissues and organs and that the aorta partakes in the general reaction, with resulting rheumatic lesions (11).

The importance of syphilis as a cause seems, on the contrary, to have been overstressed. In our series, in only 8 cases was the blood Wassermann test or the history of syphilis positive. The test was negative in 44 cases and not done in 148 unquestionable cases.

Diabetes alone ranks next in frequency as an etiologic or associated factor (12). The diabetes itself may be due to arterial changes in the viscera and in that way need not bear a purely casual relationship to the cardiac lesion. It was present in 23 cases of this series.

We have been gratified in the treatment of the cases that have their etiology in syphilis and diabetes in obtaining considerable benefit from the adequate treatment of the underlying conditions. We believe with many, in continuing intensive and persevering anti-syphilitic treatment indicated in these cases (13). Concerning diabetes, we have had a number of patients whose attacks were completely abated

in consequence of insulin therapy, after which the usual palliative measures, or nitroglycerine, for the attacks were entirely dispensed with.

It is doubtful whether tobacco and even alcohol are primary and very important causes, although I believe they cannot be excluded as contributory factors. The question remains unanswered whether the use of tobacco leads to arterial disease. If it does, it may of course provoke aortic lesions out of which angina pectoris may arise. The existence of a type of angina pectoris apparently following the excessive use of tobacco suggests the possibility of a direct relationship (14).

#### ARTERIOSCLEROSIS AND BLOOD PRESSURE

There is no other pain than that of angina pectoris which points with such deadly directness to arteriosclerotic disease (15). In an otherwise negative physical examination it is essential to search with untiring zeal for evidences of arterial changes elsewhere in the body. These will often indicate, in the absence of other signs, the underlying process producing the symptoms of angina pectoris.

Particular attention must be paid to the discovery of tortuous peripheral vessels. Careful inspection and palpation of the temporal and radial arteries should not be omitted in the clinical examination. Visualization of the retinal arteries is often a valuable clue. Capillary arterial changes are indicated by the presence of pericorneal arcus—the so-called “arcus senilis,” and by the capillary changes

in the base of the finger nail seen under slight magnification. The effects of arterial disease manifest themselves in an equally apparent way by sclerotic changes in the kidney, producing albuminuria and casts in a urine of low specific gravity.

In our series there were noted tortuous peripheral vessels in 33 cases, and definite pericorneal arcus was present in 35 cases. Albumin or casts were present in 67 of the 200 patients studied.

frequently patients with extremely high arterial tension will remain free from chest pain or angina pectoris.

As seen from Table 2, 82 cases showed a systolic pressure below 140 mm Hg which must be considered entirely within the normal, 116 had a systolic pressure above 140, the majority of these, however, were below 180. The same relation seems to hold true for the diastolic pressure. In 93 cases of this series, the diastolic pressure was below 90 mm Hg, and

TABLE II—BLOOD PRESSURE

Systolic	No Cases	Per Cent	No Died	Per Cent	Diastolic	No Cases	Per Cent	No Died	Per Cent	Pulse Pressure	No Cases	Per Cent	No Died	Per Cent
Below					Below					Below				
120	24	12	3	12.5	70	9	4.5	0	0	40	31	15.5	3	10
121-140	58	29	7	12.0	71-90	84	42	13	15	41-50	53	26.5	5	9
141-150	37	18.5	4	10.8	91-100	64	32	7	11	51-60	41	20.5	9	22
151-160	23	11.5	3	13	101-110	23	11.5	5	22	61-70	26	13	3	7
161-170	14	7	4	57	111-120	9	4.5	1	11	71-80	15	7.5	3	20
171-190	20	10	3	30	121-140	7	3.5	1	14	81-90	18	9	2	11
191-up	22	11	3	27	141-up	2	1	0	0	91-130	14	7	2	14

It is already recognized that no direct etiologic relation exists between arterial pressure and the production of angina pectoris. It is, therefore, to be reasoned that a primary increase in blood pressure is not the essential etiologic factor in the production of atheroma in the aorta or the coronary arteries. We must rather assume that this vascular area at the base of the heart in certain cases undergoes morbid changes as the result of the same toxin which produces a hypertensive effect upon the rest of the vascular system. In this relation, it is interesting to note how

in 105, above 90—the majority below 110 mm Hg. As a group, the female cases presented similar data.

Nor is there indicated from the table any particular prognostic significance of the blood pressure. The largest percentage of the cases that died had normal systolic, diastolic, and pulse pressures.

The pulse pressure as well is of little correlative importance in these cases. Of course, when seen in different phases of coronary involvement, a great variation in pressure is to be noted. The largest number of cases (94 in this series) presented

a pulse pressure between 41 and 60 mm Hg which may be considered entirely normal

The group of cases with diabetes showed no special variation from the general ratios as regards the blood pressure

### CARDIAC SIGNS

Cardiac signs are, for the experienced examiner, not difficult to recognize. But they are, in every case, a matter of interpretation. The same thrill may have several meanings, and so each of the sounds and murmurs has its own significance in any particular case. Certain signs in the physical examination of cases of angina pectoris are often dismissed, we believe, without sufficient interpretation.

#### FIRST APICAL SOUND

To the careful examiner, the quality of the first sound has an important meaning. In 62 cases, the first sound had a poor muscular quality. This is entirely a matter of individual interpretation. The muscular quality of the heart sound is of a certain pitch and volume normally. It may, of course, be exaggerated by certain nervous influences and it may be lessened under certain conditions. In cases of myocardial disease it is often much below the normal (62 of the cases). Often, it is out of proportion to what one might expect from the visible and palpable apex beat. This deficiency of the sound, when the heart beat is very marked to palpation (2 cases) is especially significant since it occurs in cases of aneurysm of the left ventricle.

In two of the patients, we observed a peculiar hollow tone, or as we have pictured it to ourselves at times, a "relaxed drum membrane" sound. This occurred in cases of serious myocardial damage.

### ROUGH SYSTOLIC MURMUR

In our series the most commonly found physical sign was a rough systolic murmur heard usually at the base. This was present in 57 cases. This murmur over the aortic area was not marked or otherwise transmitted in 20 cases. It was heard at the apex as well in 37 cases, retaining the same rough character. It was heard only at the apex in 15 other cases. When this occurs the murmur must not be interpreted as one due to mitral regurgitation, but must be considered due to disease in the aortic valve or suprasigmoid area. We believe this is quite important inasmuch as it indicates a change in the aorta when other signs of cardiac involvement to account for angina pectoris are absent. The mechanism in the left ventricle for the production of this murmur is the same as that for mitral regurgitation, although the murmur is more likely conducted toward the base in the aortic cases.

There were also found eight cases of aortic regurgitation and three cases of aortic stenosis.

### MITRAL VALVULAR SCLEROSIS

Sclerotic changes in the mitral valve are quite common. In 20% of the cases of proven coronary sclerosis both the aortic and mitral valve were the seat of sclerosis or fibrosis. The

aortic valves were alone involved in another 20% of the cases, and the mitral valves alone in 7%. The appreciation of the relative frequency of sclerosis and fibrosis of the cardiac valves associated with coronary sclerosis should aid one in interpreting the auscultatory findings, especially in older individuals. Only too often the murmur noted with cardiovalvular sclerosis is wrongly interpreted as indicating chronic valvular endocarditis.

### MITRAL STENOSIS

We have selected six cases of angina pectoris that presented the physical signs of mitral stenosis (table III). These patients all had cardiovalvular symptoms for some years prior to the onset of the angina pectoris. As indicated by the table in four of these cases, the valvular lesion followed an attack of acute articular rheumatism and is therefore to be considered of the usual rheumatic type. The diastolic blood pressure in these cases was below 100, and the systolic pressure not unusually high. In one of the patients, aortic regurgitation was associated, and the angina proved fatal within two years after the onset of the attacks.

In these cases, the electrocardiographic changes were those to be associated with mitral stenosis, and in three of these there was an inversion of the T wave in lead III. One patient had auricular fibrillation and attacks of auricular flutter, and another had paroxysmal tachycardia. Five of the cases showed characteristic tender spots on the chest wall, as in angina pectoris.

Considering the very large number of cases of mitral stenosis that we see, it is evident that only a very small proportion present the clinical syndrome of angina pectoris.

### OTHER SIGNIFICANT SIGNS AND SYMPTOMS

Of particular significance are the associated clinical symptoms that have a definite import. These consist of paroxysmal attacks of cardiac asthma, the presence of gallop rhythm at the apex of the heart, and the occurrence of cyanosis on exertion or with the attack.

Cardiac asthma cannot be directly related to angina pectoris. It occurred only in those ten patients who already showed very extensive myocardial disease. Five of these patients died. It is therefore a phenomenon associated with the advanced changes following coronary thrombosis, rather than with angina pectoris as a clinical picture. It may be considered, like *pulsus alternans*, a manifestation of myocardial damage. In our series of cases, 13 cases showed marked *pulsus alternans*, 4 with cardiac asthma and 6 of which terminated fatally.

The occurrence of systolic gallop rhythm is a clinically ominous sign. It is an indication of myocardial deficiency and is usually associated with other evidences of beginning heart failure. It occurs more frequently in diffuse myocardial lesions and is probably parallel in its implication to the occurrence of *pulsus alternans* in cases of hypertension. Under adequate treatment by rest and cardiac stimulation, it may subside and re-

TABLE III—MITRAL STENOSIS GROUP

Name and Sex	Age of Onset of Angina	Tonsillitis	Rheumatism	Symptoms of heart lesion	Blood Pressure	Associated Conditions	Electrocardiogram	Tender Spots	Mortality
F B F	51	+	Acute articular	30 yrs	146 92	Tenderness over gall bladder region	T wave slightly inverted in lead III	Gall bladder tenderness	
L C M	38	+	Muscular pain	5 yrs	132 84	Paroxysmal tachycardia Congestive nephritis	P wave notched in lead III, peaked in leads I and II	Precordium Right pectoral region	
J G M	45	o	Acute articular	32 yrs	130 70	Aortic regurgitation Tortuous vessels Chronic nephritis	o	o	+
B K F	39	o	o	14 yrs	104 94	Auricular fibrillation or flutter Pulmonary asthma Congestive nephritis	Right ventricular preponderance Auricular fibrillation and flutter	Sternal spots	
L S F	38	+	Acute articular	3 yrs	152 100	Pulmonary asthma Congestive nephritis	P wave notched in lead II T wave inverted in lead III	Precordial Epigastric	
J W M	42	+	Acute articular	7 yrs	154 96	Congestive nephritis	Left ventricular preponderance. P wave wide in lead II T wave inverted in lead III	Precordial	



appear only as evidence of increasing cardiac embarrassment

With coronary closure, a very characteristic and most important sign is the peculiar hue of the skin that develops. It had been described by Sansum several decades ago in association with aortic valvular lesions, but no doubt was due, as we now know, to the coincidence of coronary thrombosis (16). The color consists of a sallow pallor with an ashen gray or leaden cast. It invariably signifies the closure of a branch of the coronary artery with myocardial infarction, and on that account bespeaks a grave prognosis.

Another important sign is that which we have observed at the time of the occurrence of coronary closure, i. e., the presence of definite cyanosis during an attack of angina pectoris. Ordinarily, with the attack the associated vasomotor changes produce extreme pallor with, perhaps, a cold sweat. But when cyanosis takes place, it implies a great cardiac embarrassment and is doubtless, as we have found in our cases, the result of coronary closure.

#### GALL BLADDER DISEASE

The relation of angina pectoris to gall bladder disease requires careful clinical consideration. The symptom in common between the two is pain, often distressing, and localized in the epigastric region. We believe that the diagnosis may be made both of angina pectoris and gall bladder disease when symptoms pointing to both conditions are present. We are fortified in this assumption by the anal-

ysis of Willhus in which he found chronic cholecystitis, with or without stones, in 26% of proven coronary cases. This high incidence is due to the fact that gall bladder affection manifests itself in middle or later life when arterial degenerative changes become evident. The error most often committed is one of omission, where the gall bladder disease is neglected and the diagnosis is made of angina pectoris alone.

In our series, gall bladder disease was associated with angina pectoris in ten of the 200 cases.

#### ELECTROCARDIOGRAPHIC STUDIES

The constant presence of myocardial changes in cases of coronary involvement would lead one to suppose that the electrocardiogram would be of great assistance in diagnosis. Of course, if we were to expect spectacular changes in the electrocardiogram in every case we would find ourselves not fully satisfied. Looking at it critically, however, one is not disappointed. It is true that occasionally, where the clinical symptoms are prominent, the electrocardiogram will appear normal, or again, when the patient is in apparent good health, the electrocardiogram will be gravely informative.

The changes that take place in the electrocardiographic picture immediately after coronary thrombosis will naturally vary with the location of the involved coronary vessel and the size of the branch. (Compare figs 1 and 2.) Certain characteristic alterations develop in different cases because of the greater frequency of clos-

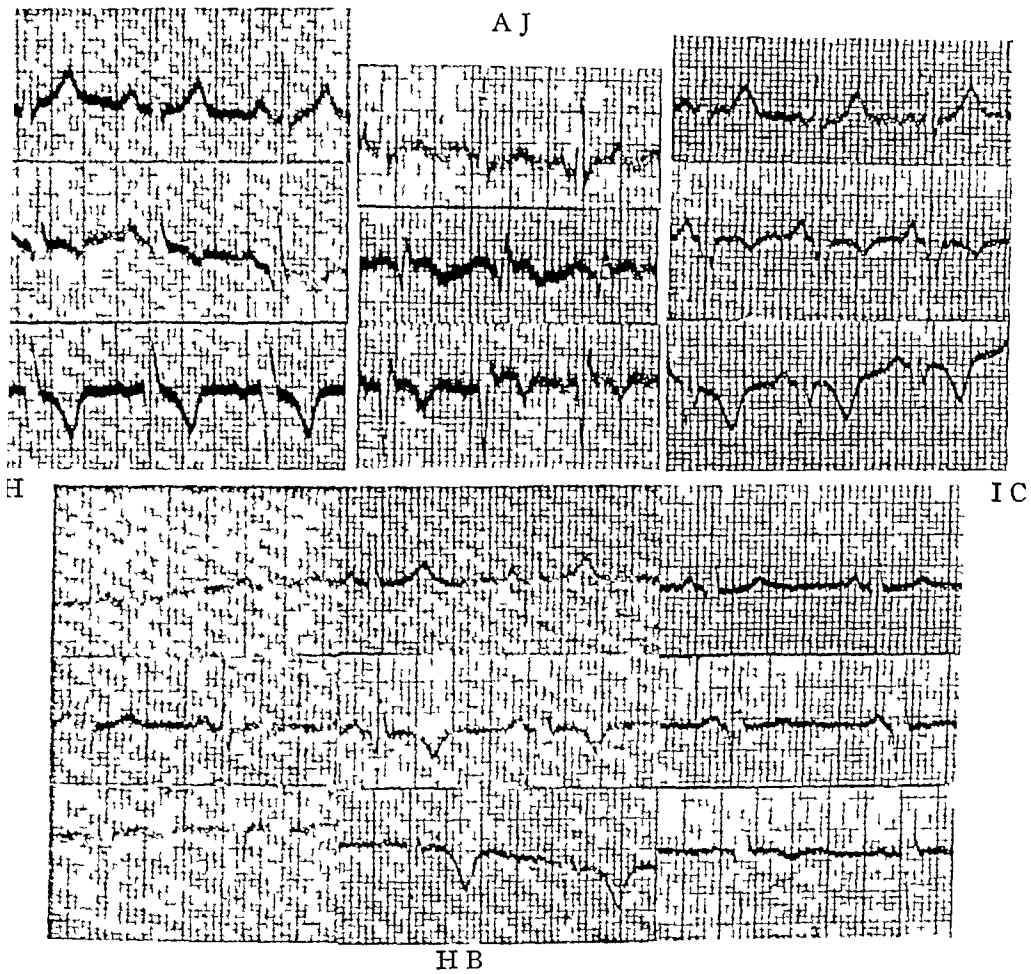


FIGURE 1—Four cases showing characteristic inversion of the T wave in leads II and III after a severe attack of angina pectoris  
 Case J H—Four days after severe attack, 18 months after onset  
 Case A J—Three weeks after first attack Sudden cardiac death two months later  
 Case I C—One week after first attack  
 Case H B—Six months after onset of pain  
 Eight months later—one week after first attack  
 Eighteen months later—cardiac death six months later

of the anterior descending branch of the left coronary (17). It is probable that a comparable series of pathologic changes takes place within a variable period of time. With extensive infarction of areas in the heart and especially of the endocardial regions, more marked electrocardiographic evidence is produced, such

as bundle branch block, QRS widening and notching, etc.

Transitory electrocardiographic effects may be produced in organic coronary lesions where the coronary closure was not complete (Fig 3). They may also occur synchronously with functional changes in the coronary circulation (18).

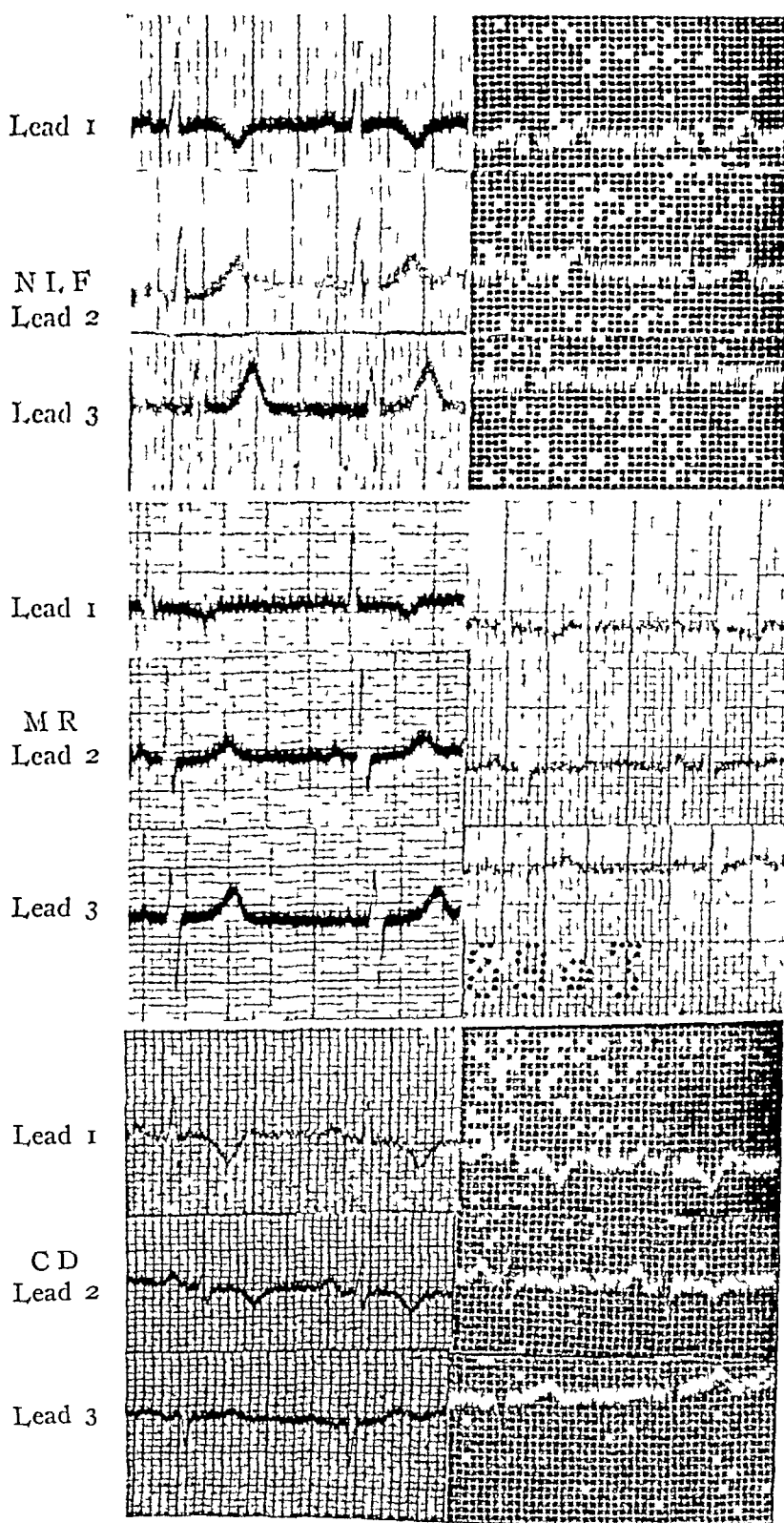


FIGURE 2—Three cases showing characteristic inversion of the T wave in lead I after severe attack of angina pectoris  
 Case N L F—Two weeks after his first severe attack  
 Four years later  
 Case M R—One month after his first attack  
 Three years later  
 Case D D—Three weeks after first severe attack  
 Two and a half years later—no intervening severe attacks

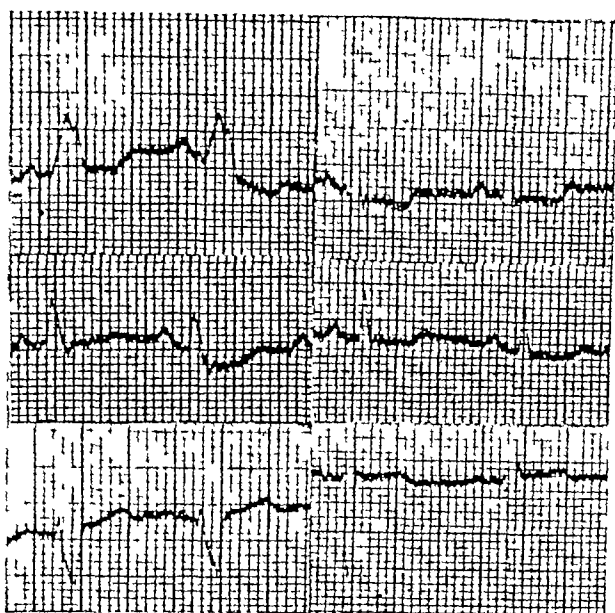


FIGURE 3—Case R H, five weeks after her first severe attack  
One year later—no intervening attacks

Of the 200 patients examined, a rather broad analysis was made of the electrocardiographic films. An exact tabulation could not be made for the reason that in many cases repeated films were recorded at intervals of months and years, and these often showed remarkable differences one from the other. However, certain general results can be analyzed from the table (table IV).

There were 110 cases with left ventricular preponderance and only six cases of right ventricular preponderance, while 58 had no ventricular preponderance. The mortality was not appreciably greater in any one of these groups.

It would seem that the importance of widening of the QRS wave, which indicates a time obstacle in the conduction of the stimulus, is equal in its significance to the notching and thickening of the QRS wave, even when it is present in lead III. As

is to be seen, of each of the groups showing either of these changes, six or 25% died.

Judging from the table, the prognostic significance of low voltage is not as great as of high voltage in the cases of angina pectoris. Of the seven cases with high voltage, 42% died, of the eight cases with low voltage, 25% died (19).

Inversion of the T wave in leads I and II, and in leads II and III are of equal significance, although a smaller number of the cases showed these combined changes. The T wave was inverted in lead I alone in 22 cases, and in lead III alone in 53 cases. But the fatalities that occurred were greater in percentage when the T wave was inverted in two leads simultaneously.

Of course, with bundle branch block and heart block, which indicate extensive myocardial changes involv-

TABLE IV—ANALYSIS OF ELECTROCARDIOGRAMS

	Number	Number Died	Percent Died
Left ventricular preponderance	110	12	11%
Right ventricular preponderance	6	1	16%
No ventricular preponderance	58	10	17%
Sinus bradycardia	2	1	50%
Sinus tachycardia	3	1	33%
P wave inverted, notched, or widened	22	2	9%
QRS wave notched and thickened	22	6	27%
QRS wave widened	24	6	25%
Extrasystoles—Auricular, ventricular, nodal	15		
Bundle branch block	3	2	66%
Complete heart block	1	1	100%
T wave inverted in lead I only	22	1	4%
T wave inverted in leads I and II	7	2	28%
T wave inverted in lead III only	53	5	9%
T wave inverted in leads II and III	10	2	20%
Low voltage of QRS complex	8	2	25%
High voltage of QRS complex	7	3	42%
Electrocardiogram negative	12	2	16%

ing the subendocardial tissues, the mortality was very high

It is well known that electrocardiographic changes follow promptly upon an attack of angina pectoris associated with coronary closure (20) In the series of prints shown in Fig 1 and 2, the time relation is indicated between the attack of angina pectoris, implying coronary closure, and the electrocardiograms taken The electrocardiograms, arranged in a series, show the changes that take place with infarction and with reparation Sharp inversion of the T wave may take

excite, and the conspicuous changes that are so apparent (fig 4)

MORTALITY

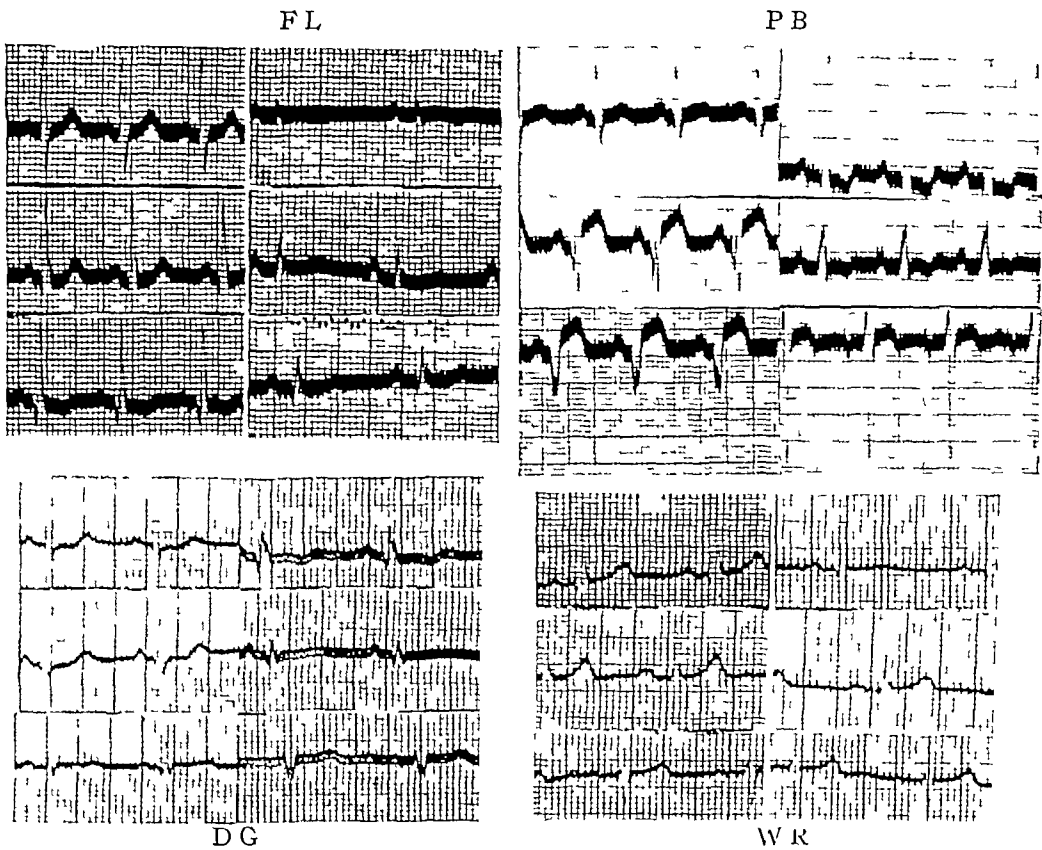


FIGURE 4—Case FL, four months after first attack—two days after severe attack  
Three months later—five days after severe attack

Case PB—Four weeks after onset

Ten days later

Case DG—Five years after first attack, one week after third severe attack

One year later, six months after last severe attack

Case WR—One week after first attack

Three months later

on for a long time unobtrusively and death result only when the lesion is well advanced at a later age. However, in 13 of the patients who died after a relatively short time of clinical angina pectoris, there were present prodromal symptoms that had lasted from one to ten years. This emphasizes the importance of giving attention to the prodromal symptoms of cardiac arteriosclerosis.

The electrocardiograms in the cases that died were also very instructive. In a few of these no other evidence

of myocardial damage was present except left ventricular preponderance. However, in a large number, there was notching of the QRS wave, inversion of the T wave in leads I and II, or II and III, or in either I or III. QRS notching and widening was quite common. Two cases showed bundle branch block, and one case presented heart block.

#### SPECIAL METHODS OF TREATMENT

Of recent years, palliative measures have been used in some cases with

considerable benefit for angina pectoris. These consist of methods which endeavor to reduce the amount of pain felt, either by actually altering the pathologic process in the aorta and coronaries, or by blocking the pain stimuli from the diseased area. In the first instance, I refer to the use of diathermy.

DIATHERMY

Diathermy is a form of treatment in which heat is generated in the tis-

sues by the passage through them of high-frequency currents. It is essentially different from the warming of a part or the application of heat to the skin. Human tissues are conductors of an electric current, but they are conductors with a high resistance, and consequently the passage of an electric current through them generates heat. In February, 1912, Nagelschmidt published his classical paper in the Roentgen Ray Archives on the diathermic treatment of circulatory disorders, re-

TABLE V—DECEASED GROUP

Name and Sex	Age at Onset	Age at Death	Duration	Time of Prodromal Symptoms	Electrocardiogram	Significant Signs and Symptoms
I B F	48	54	6 yr	0	Extrasystoles	Aneurysm heart?
P B M	54	54	1 mo	0	Left ventricular preponderance QRS wave notched T wave inverted in leads I and II	
M B M	50	52	2 yr	9 yr	T wave inverted in Lead I QRS wave notched and widened	
H B M	46	49	3 yr	0	Three successive electrocardiograms showing coronary closure	Cyanosis at times
P C M	54	57	3 yr	0	QRS wave notched and widened T wave shows low voltage	Pulsus alternans Cardiac asthma
L F F	58	59	1 yr	3 yr	Right bundle branch block Arborization block	Pulsus alternans Cardiac asthma
A G M	36	43	9 yr	0	Left ventricular preponderance	Cyanosis at times
J G M	45	47	2 yr	0	0	Mitral stenosis Aortic regurgitation
A H M	45	17	2 yr	0	Negative	Wassermann ++++

TABLE V—CONTINUED

Name and Sex	Age at Onset	Age at Death	Duration	Time of Prodromal Symptoms	Electrocardiogram	Significant Signs and Symptoms
G H M	57	61	4 yr	11 yr	0	Cardiac asthma
A J M	65	65	3 mo	0	Left ventricular preponderance T wave inverted in Leads II and III	Auricular fibrillation Aortic stenosis
I L M	52	54	2 yr	2 yr	Left ventricular preponderance	Gallop rhythm
S L M	39	41	2 yr	0	Left ventricular preponderance T wave inverted in lead III QRS wave notched and widened	First sound much weaker than diffuse impulse
A L M	61	61	6 mo	15 yr	Left ventricular preponderance T wave inverted in leads II and III	
J M M	33	39	6 yr	0	0	Pulsus alternans Cardiac asthma
R M F	75	76	1 yr	0	0	Auricular fibrillation Sudden death
G M M	56	64	8 yr	2 yr	P wave wide and diphasic in lead III QRS wave diphasic in leads II and III T wave inverted in leads II and III	Sudden death
S M M	46	47	1 yr	8 yr	Left ventricular preponderance	Aneurysm of left ventricle
J P M	65	65	3 mo	1 yr	Left ventricular preponderance T wave inverted in lead III	
I P M	56	59	3 yr	0	Right bundle branch block	<i>Pulsus alternans</i>
I P M	50	52	2 yr	0	T wave inverted in Lead I	Hypertension Cerebral arteriosclerosis
M R M	40	49	9 yr	0	Right ventricular preponderance Low voltage P wave notched in lead I and high and wide in lead II	Frequent cyanosis Cardiac asthma Cheyne-Stokes respiration





interrupt the course of the afferent fibres from the heart

The great importance of the relief of pain arises not alone in the fact that the patient's suffering is reduced, but more especially in the fact that the patients with angina pectoris may die as a result of the pain by cardiac inhibition through the vagus. It must be remembered that a diseased heart is more responsive to vagus influence than a normal one (23)

In one method alcohol injection is made into the posterior ganglion of the lower cervical and upper dorsal spinal roots (24). Section of these roots has not been attempted, but extirpation of the sympathetic cervical chain has been done in a large number of cases. In these, various parts of the sympathetic ganglion were removed, the stellate ganglion being removed in some cases on one or both sides, and the upper or middle sympathetic ganglion in other cases. Jonnesco extirpated the entire cervical chain (25). Danielopolu sectioned the cervical sympathetic chain above the stellate ganglion and injected with alcohol the ganglia of the spinal nerves (26).

No uniform result has been obtained and more complete relief reported in those cases in which most of the sympathetic cervical chain has been removed on both sides. The reports in general from each of these methods are quite favorable inasmuch as the attacks of severe precordial pain are considerably relieved and often the freedom from pain is present for months (27). Most patients of our series of cases have, however, been able to keep more or less comfortable

under our observation, employing nitrates, avoiding strain, taking a light diet, and requiring occasional sedatives for the discomfort.

We feel justified in classifying our series of cases into the following groups

- 1 Angina pectoris due to aortic disease
  - a Prodromal cases
  - b With hypertension
  - c With aortic atheroma
  - d With aortic regurgitation
  - e With aneurysm of the aorta
  - f With aortic stenosis
  - g Other pathological lesions that may exist
- 2 Angina pectoris with coronary disease
  - a With coronary arterial spasm
  - b Left coronary involvement
  - c Right coronary involvement
  - d Coronary capillary involvement
- 3 Angina pectoris with rheumatic disease
  - a Rheumatic myocarditis
  - b Mitral stenosis

Though we recognize the incompleteness and inadequacy of such a classification, we believe that it is only with a classification conceived on some organic basis that the newer problems in the study of angina pectoris can be undertaken with more discerning scrutiny.

#### SUMMARY

1 Two hundred cases of angina pectoris are critically discussed

2 The name "pseudo angina pectoris" is indefensible and should be dismissed from the cardiologic nomenclature

3 Angina pectoris often presents various prodromal symptoms which indicate that the cardiac process preceding the attacks of angina pectoris is a prolonged one, and that the appearance of angina pectoris suggests a more or less developed pathology in the aorta and coronary artery

4 Hyperesthesia, or tender spots on the chest wall, may serve as a differential diagnostic point from intra-abdominal disease

5 The immediate cause for the attacks of angina pectoris is classified according to the possible pathological conditions that may exist

6 Almost 22% of the cases had their first typical attacks before the age of 40

7 Rheumatism and diabetes appear to factor importantly in the etiology

8 Arteriosclerotic disease is the outstanding condition in angina pectoris as indicated by the tortuous peripheral and retinal vessels, the presence of pericorneal arcus, and arteriosclerotic renal changes

9 There seems to be no direct etiologic relation between arterial blood pressure and the production of angina pectoris

10 The most commonly found physical sign in angina pectoris was a rough systolic murmur due to aortic change

11 Angina pectoris was associated with rheumatic mitral stenosis in six cases

12 Of particular prognostic significance are the associated clinical symptoms of cardiac asthma, pulsus alternans, systolic gallop rhythm, and the occurrence of cyanosis on exertion or with an attack

13 The differential diagnosis of angina pectoris from gall bladder disease is discussed

14 The electrocardiographic picture in angina pectoris is analyzed in detail

15 Thirty patients of our series died from angina pectoris. In these the age of onset bore a distinct relationship to the duration of life—the later the onset, the worse the prognosis

16 Palliative and surgical measures in the treatment have proven of considerable value in selected cases

17 A classification of angina pectoris is presented conceived on an organic basis which may serve for further study

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# Congenital Atresia of Aortic Ring\*

By NEWELL PHIBBS, M.D., C.M., *Chicago, Illinois*

ALL congenital cardiac defects belonging to the cyanotic group, true morbus caeruleus, must be considered as very grave conditions. Perhaps the most serious of this group are those cases showing atresia or aplasia of the valvular orifices on the left side. These individuals usually die during the first few days of life and it is necessary for a compensatory anatomical adaptation to be present in order to maintain life even for a short time.

Atresias on the left side have, associated with the anomaly, defects in the ventricular auricular septum, as well as a widely patent ductus Botalli. The left ventricular cavity is very small and the wall shows an eccentric hypertrophy. There is an accompanying small left auricle. The right ventricle and auricle are enormously dilated and hypertrophied. Usually the right ventricle is crescent shaped and surrounds the whole lower portion of the left ventricle, thus causing the apex to be entirely formed by the right heart. Invariably the pulmonary artery is greatly enlarged in direct contrast to the ascending portion of the aorta which is markedly hypoplastic. Often we have accompany-

ing anomalies in other parts of the body such as transposition of the viscera, an absent spleen or kidney.

Many varied theories have been advanced in regard to the etiology of cardiac defects. However, we can be safe in dividing these anomalies into two definite groups with reference to their cause—I, arrest of growth, II, fetal disease. Undoubtedly a large percentage is caused by some disturbance in development at different stages of fetal life. On the other hand, we can prove conclusively that cardiac anomalies are frequently caused by some inflammatory or degenerative process being present during fetal life. It has been shown that syphilis plays a very active part in the causation of many cardiac defects.

Previously it was thought that fetal endocarditis played the most active part in fetal disease and that myocardial changes were of little significance. In recent years microscopic pathology has proven that myocardial disease is by far the most common cause of cardiac anomalies excluding those due to primary arrest in development. Abbott states, in a very masterful discussion regarding the etiologic factors of cardiac defects,—“Fetal endocarditis probably occupies a very minor rôle, being limited to those relatively few cases in which a rheumatic

\*From the Pathological Laboratory, University of Michigan, Ann Arbor

endocarditis is directly transmitted from the mother to her offspring. Of far greater importance are undoubtedly the myocardial changes which occur as a result of congenital syphilis or other infection carried in the coronary stream." Most cases of atresia of the orifices reveal in the myocardium different degrees of degeneration, vacuolation, fatty change, and diffuse fibrosis often myxomatous in character, very similar to that described by Warthin as "focal fatty degeneration associated with localized colonies of *spirochaeta pallida*." Observations by von Zalka in six cases of atresias or stenosis of the aortic and pulmonic orifices agree with the above findings. In every case of this group definite myocardial changes are found.

Aortic atresia is not common. Those forms due to lack of development are distinguished from those caused by inflammatory processes. The inflammatory forms are the more frequent, occasionally due to fetal endocarditis with fusion of the cusps but more often due to a diseased myocardium with a narrowing of the conus and obliteration directly below the orifice. Simmon's report states that the infant attained an age of sixteen weeks but this subject is the oldest on record, the average age being approximately three weeks. Undoubtedly there have been many similar cases which perished during fetal life or shortly after birth and were never recognized.

The literature contains six cases of aortic atresia. To this we add the present communication—a case of aortic and mitral atresia associated

with a widely patent foramen ovale and a dilated ductus arteriosus.

*History of Case* The mother came to hospital 5-20-28 stating that she was pregnant and that her last menstrual flow was in August 1927. Physical examination showed her to be very near term. She was a well nourished individual, seventeen years of age and married. No previous pregnancies or miscarriages had occurred. There was no clinical evidence of syphilis and her blood Wassermann was negative. She had always been in excellent health.

Labor began at 10 P. M., 5-21-28, and lasted seventeen hours. Presentation was a complete breech. The feet were delivered by the Pinard maneuver and the body was delivered spontaneously. Weight at birth was 2820 gms.

Immediately after delivery the child breathed and cried naturally. There was a slight cyanosis of the nails and mucous membranes but the skin of the body was a natural pink. Externally there were no deformities or abnormalities with the exception of the scrotum which was red and swollen. The following day the infant was apparently progressing favorably and no cyanosis was noted. From the start it took to the breast poorly but otherwise gave no cause for alarm until the second morning when cyanosis was first noted. This symptom appeared gradually and steadily increased in intensity. At first, only the extremities and mucous membranes were affected but soon there was a generalized bluish discoloration of the whole body surface. Oxygen was administered every alternate ten minutes but with no good result. The infant was carefully examined at this time. Very rapid and slightly irregular heart sounds were heard but there was no suspicion of a congenital heart lesion being present. Intermittent dyspnoeic attacks began to occur late in the second day and recurred at intervals until death one day later. During these attacks of respiratory embarrassment the cyanosis became much more marked. Death took place 5-25-28, sixty-two hours after birth.

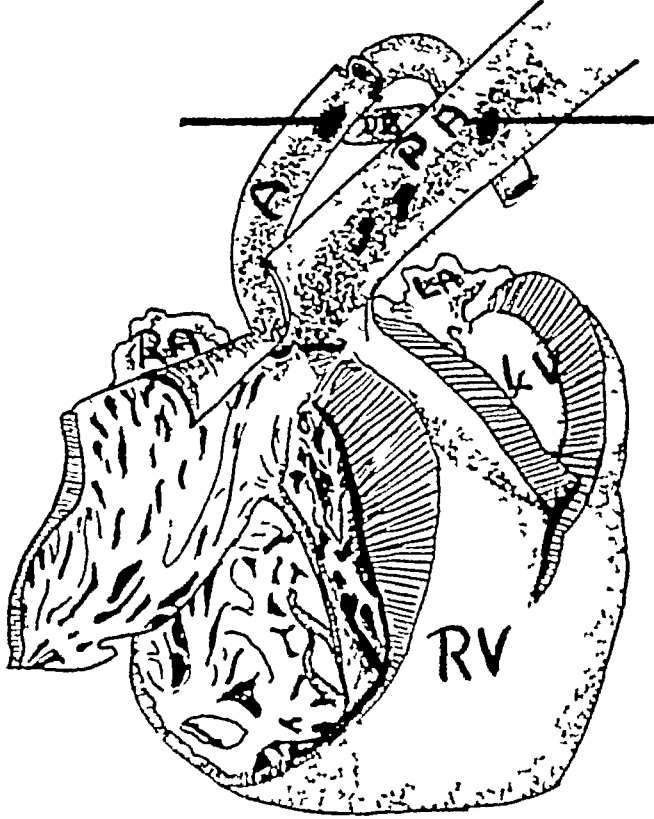
Wassermann reaction on the cord blood was negative.

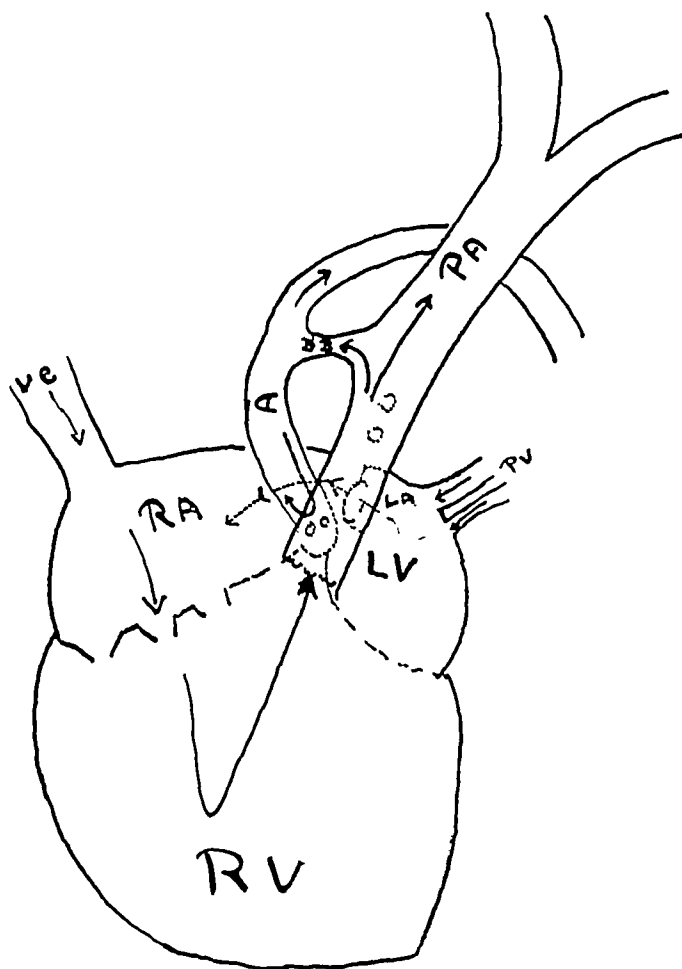
Autopsy performed 20 hours after death  
Protocol (abbreviated) Baby M Sex—  
Male Age 62 hours

*External Examination* Body is that of  
a well developed male infant 47 cms in  
length and weighing 2670 gms Nutrition  
appears good The head is symmetrical  
and measures bi-parietal diameter  $9\frac{1}{2}$  cm

All the viscera are in normal positions and  
no abnormalities are noted

*Thoracic Cavity* The lung borders are  
2 cm apart in the anterior mediastinum  
Heart lies transversely to the left of the  
mid-sternal line with the apex in the 4th  
intercostal space well outside the mid-clav-  
icular line and pointing toward the left





No II

Diagram to illustrate the flow of blood. Direct communication between the left and right auricles through foramen ovale. Also a widely patent ductus arteriosus joins the pulmonary artery to the aorta. Note the coronary openings above the fusion in the aortic ring. (Diagram by Miss Dorothy Wheeler.)

ing in the mitral region with the endocardium smooth and shining. A direct communication between the left and right auricles is established by means of a widely patent foramen ovale. The diameter of the opening measures 9 mm. On opening the heart the left ventricular cavity is found to be greatly diminished in size with no natural opening present, the mitral orifice is completely sealed and there is a complete atresia of the aortic ring. The muscle wall appears somewhat hypertrophied.

*Right Heart.* Right ventricular wall appears hypertrophied. Both cavities are enormously distended. It is noted that the

right ventricle practically encircles the left ventricle and the right cavity is crescent shaped. No opening can be found in the interventricular septum. The endocardium is smooth and shining. Tricuspid valve is well formed with no thickening of the cusps. There is a marked increase in calibre of the pulmonary orifice but the cusps are three in number and appear normal. On tracing the vessel upward a widely patent ductus arteriosus is found with the opening 4 cm from the pulmonary valve. The ductus opening measures 6 mm and the total length is 8 mm. The pulmonary artery is enormously dilated but appears



normal otherwise There is a branch to each lung and no anomalous vessels are noted

*Coronary Vessels* Two small openings about 1 mm in diameter are found near the blind end of the aorta A small probe can be passed into the lumen of either coronary vessel

*Aorta* Is hypoplastic throughout its whole course but markedly so in the ascending portion and in the arch The opening of the ductus is in the arch near the descending portion Diameter of the opening is 5 mm

*Lungs* Are air containing There is a marked congestion throughout with a partial atelectasis in the lower lobes

#### MICROSCOPIC FINDINGS

*Spinal Cord* There is no evidence of syphilis

*Cerebrum* Congestion and edema is marked No localized lesions are present

*Heart* No evidence of syphilis is found Muscle is well developed Endocardium shows a marked thickening apparently as it approaches the aorta with complete obliteration of one vessel and nearly complete obliteration of another

*Lungs* Contain very little air The majority of the alveolar spaces are not dilated There is extreme congestion and edema with multiple petechial hemorrhages (Death by asphyxia) There is no evidence of pneumonia The fat stains show numerous fat droplets, finely divided in the alveolar spaces

*Thyroid* A small amount of colloid is present with exception of scattered areas where it is unusually abundant for a child three days old

*Thymus* There is hyperplasia of the medullary portion with numerous corpuscles of Hassall The lymphoid portion is not hyperplastic

*Spleen* Shows marked congestion Some of the follicles have central lymphoid exhaustion

*Liver* Is an extreme nutmeg liver with marked central necrosis and fatty degenerative infiltration Fat stains show marked fatty degenerative infiltration

*Adrenals* The medulla is hypoplastic There is a slight lipoidosis of the cortex

*Kidneys* Show congestion and slight cloudy swelling (probably post mortem) Fat stains show marked lipoidosis of the loops of Henle

*Pathological Diagnosis* Congenital atresia of aortic ring with absence of aortic valve. Atresia of mitral valve Patent foramen ovale Dilated pulmonary artery with patent ductus arteriosus Hypoplasia of left auricle and ventricle Hypoplasia of aorta Extreme congestion, oedema and hemorrhage by diapedesis in lungs Pronounced nutmeg liver Hyperplasia of thymus Hypoplasia of adrenals Generalized passive congestion Asphyxia

#### DISCUSSION

From the clinical aspect a few features should be emphasized Diagnosis of congenital heart disease in the early stages of life is at all times very difficult and often impossible Though the clinical findings in this case are very definite there are two conspicuous features, cyanosis and dyspnoea, which are present at some stage of life in most cases of a similar nature

Cyanosis in the majority of aortic atresias is very marked but one should never be misled by the absence of this sign Peacock cites different examples of congenital defects where venous and arterial blood are freely mixed and there is no cyanosis evident The causative factors of cyanosis are fully discussed and very adequately summarized by Abbott under the two headings of modifying and determining factors The determining factors produce cyanosis by directly raising the concentration of reduced hemoglobin in the capillary stream above its "threshold-value," while the modifying factors may alter the degree of cyanosis but cannot by

themselves produce an increase in oxygen unsaturation. In the present case cyanosis was not marked during the first two days but it became very pronounced in the last 20 hours of life.

Dyspnoea is also a very frequent symptom in this group, especially when cyanosis is marked. It does occur, however, when no trace of cyanosis is seen and apparently there is no definite relationship between these conditions. In the terminal stages many individuals have marked dyspnoeic attacks which are accompanied by marked increase in the cyanosis. This feature is well demonstrated by the present history.

Often a harsh, systolic, machine-like murmur, accompanied by a thrill, is localized to the upper precordium in cases of patent ductus. On careful examination the clinicians were not able to elicit any such findings in the above case.

The pathologic picture gives no evidence of myocardial involvement. The endocardium is definitely thickened in the left ventricular cavity but there is no other proof of an inflammatory process. Syphilis cannot be suspected after careful microscopic examination of the different organs and of the cord and placenta. No other infective process is present in any of the viscera. We may conclude that this case appears to belong to that group of cardiac defects caused by arrest of development.

To summarize we have

- 1 A case of aortic and mitral atresia which survives for 62 hours
- 2 Cyanosis and dyspnoea are the prominent clinical features
- 3 There is no definite evidence of an inflammatory process and the defect is probably due to arrest of development in fetal life

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# Krysolgan in the Treatment of Lupus Erythematosus: Report on Twenty-eight Cases\*

By WILLIAM H. GORCKIRMAN, M.D., *Section on Dermatology and Syphilology, The Mayo Clinic, Rochester, Minnesota*

IN the treatment of lupus erythematosus it is probably too much to expect that any one method will act as a specific in all forms of the disease, although it can be said without hesitation that since the disease is the result of an internal toxic process, its attack by the internal and systemic route is more logical than by any local application. Many drugs have been used in the former manner, but only a few, and these probably not very effective, have attained reasonable popularity. Since the gold preparations were first used about fifteen years ago, they have gained in popularity, and for the last three or four years in this country they have been widely discussed, but use of the preparations has been delayed by the European reports on their toxic and even lethal effects. Krysolgan is seemingly the preparation most popular in Europe, and since Schamberg and Wright (1) published their report on the use of gold and sodium thiosulphate, this

preparation has apparently become the choice in America. I have employed both, but since my experience with krysolgan has been greater I shall confine my discussion here to this drug.

Although I have used krysolgan in the treatment of twenty-eight cases, I shall only abstract a certain number of cases in which the results can be objectively demonstrated. In a critical estimate of the value of the drug the entire series will be considered.

## ABSTRACT OF CASES

*Case 1*—A man, aged forty-three, first noticed chronic discoid lupus erythematosus in October, 1925. There were no demonstrable septic or tuberculous foci. The patient was treated by the injection of foreign protein, by the application of roentgen ray to the gland-bearing areas, by the administration of quinine and iodoform for the constitutional effect, carbon-dioxide snow, lotio alba, and 3 per cent ichthyol ointment were applied locally. None of these measures produced a satisfactory response. Krysolgan was then given, this being the first time the drug was used in The Mayo Clinic. The results are shown in figure 1.

*Case 2*—A woman, aged thirty-two, first noticed the lesion in February, 1926. On examination at the clinic infected tonsils were noted but no evidence of tuberculosis. Krysolgan was given with healing of the

\*Submitted for publication April 26, 1928.

<sup>1</sup>Schamberg, J. F. and Wright, C. S. The use of gold and sodium thiosulphate in the treatment of lupus erythematosus. *Arch. Dermat. and Syph.*, 1927, xv, 119-137.

lesion The tonsils were removed before her dismissal Local treatment by ultra-violet light and roentgen ray had been given elsewhere (fig 2)

*Case 3*—A woman, aged twenty-five, first noticed the lesion on the bridge of the nose in June, 1926 Later two small patches appeared on the left cheek There were no demonstrable pyogenic or tuberculous foci Mild local applications were applied before krysolgan was given It developed subsequently that the patient was in the first month of pregnancy when krysolgan was begun, but no untoward symptoms resulted (fig 3)

*Case 4*—A woman, aged sixty-one, first noticed the lesions in 1914 On examination at the clinic dental sepsis and old tuberculous lesions of both upper lobes were found Various methods of treatment were ineffective but krysolgan was given with improvement ((fig 4)

*Case 5*—A woman, aged forty-eight, first noticed the lesions in 1921 Examination did not reveal demonstrable septic foci, but an old tuberculous lesion of the upper lobe of the lungs was noted She had been treated by radium, Kromayer light, carbon-dioxide snow, and various medicinal applications locally, quinine internally, and roentgen rays for their systemic effect, before krysolgan was given There was satisfactory response from krysolgan only (fig 5)

*Case 6*—A man, aged thirty-four, first noticed the lesion in 1920 His tonsils were infected but there was no evidence of tuberculosis Treatment had consisted in large doses of quinine before the krysolgan was given The response in this case was rather slow but finally very satisfactory (fig 6)

*Case 7*—A man, aged thirty-three, first noticed the lesion in 1921 There were no demonstrable septic or tuberculous foci Treatment had consisted of the injudicious use of radium and roentgen rays to the point of marked atrophy and telangiectasia without materially affecting the lesion Treatment by the administration of krysolgan produced satisfactory response (fig 7)

*Case 8*—A woman, aged twenty-three, first noticed the lesion in 1917 There were no demonstrable septic or tuberculous foci Various methods of treatments had been instituted both for local and for systemic effect, all were unsatisfactory Krysolgan was begun in October, 1927, the results were satisfactory (fig 8)

#### METHOD OF TREATMENT IN THE CASES ABSTRACTED

Cases 1 to 5 show complete involution of the eruption in the sense that not a vestige possibly denoting inflammatory reaction remained All the erythema, scaling, crusting, and epithelial plugging disappeared and only a smooth white scar, with possibly faint telangiectasia in an occasional case, remained In Cases 6 to 8 the objective result was not quite so satisfactory Radium had been applied to the point of permanent injury to the skin While all active inflammatory reaction had subsided it was especially difficult to determine how much of the final condition of the lesion was due to the radium treatment and how much was due to the lupus erythematosus

In Case 1 twelve injections were given of approximately 0.5 gm., a minimal dose of 0.0001 gm and a maximal of 0.05 gm The intervals between injections varied from nine to fourteen days Considerable caution was exercised since this was the first case treated In later cases the dosage was materially increased and the time interval decreased It was particularly noticeable, after more experience that the small dosage had given excellent results In Case 2 eighteen injections, a total of 0.6 gm were given at weekly intervals This was



FIGURE 1—Before and after treatment



FIGURE 2—Before and after treatment



FIGURE 3—Before and after treatment

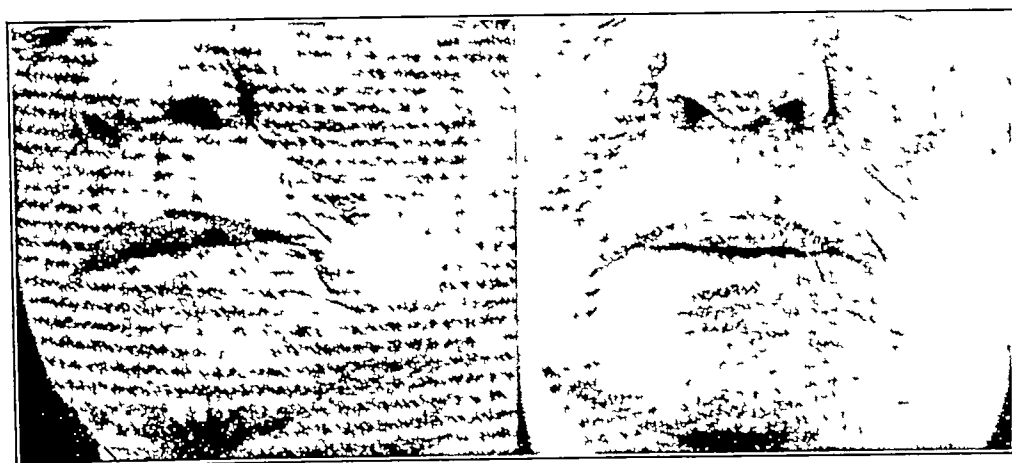


FIGURE 4—Before and after treatment



FIGURE 5—Before and after treatment



FIGURE 6—Before and after treatment

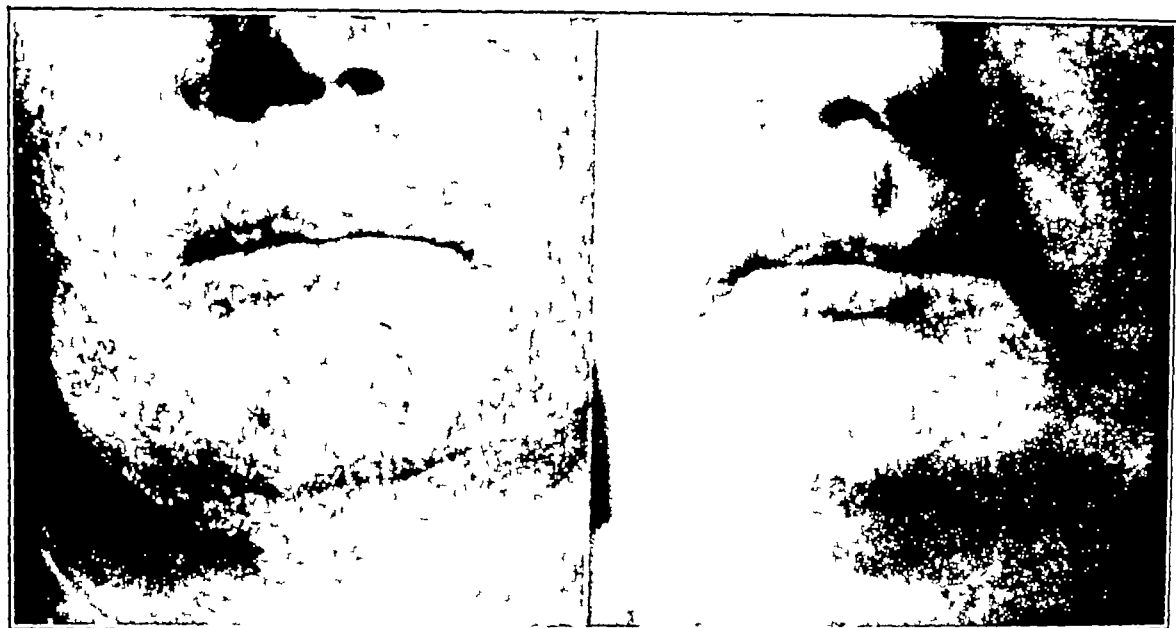


FIGURE 7—Before and after treatment



FIGURE 8—Before and after treatment

the fifth case in the entire series. It may be noted that the total dosage amounted to more than ten times that given in Case 1. In Case 3 a total of 10 gm was given in twenty-seven injections. The injections were at first given once a week and later twice a week. The drug was well tolerated. In Case 4 a total of about 0.52 gm in fourteen injections was given at intervals of from three to seven days without incident. In Case 6 a total of about 1.5 gm in thirty-three injections was given at intervals of from one to two weeks without

difficulty. In Case 7 a total of 14 gm in thirty injections was given twice a week throughout the period of treatment without incident. In Case 8 a total of 10 gm in twenty-five injections was given three times a week during the period of treatment without incident. These cases represent treatment schedules varying considerably in intensity according to the patient, total dosage and time interval, yet the results have been equally good and none of the patients showed sensitiveness.

TREATMENT IN THE REMAINING  
CASES IN THE SERIES

One or two injections were given in three of the remaining twenty cases. The results in these are of no significance in establishing the therapeutic value of the drug. Two patients discontinued treatment for irrelevant personal reasons, and one showed marked hypersensitiveness to one minimal dose. In the latter case the lesions tended toward dissemination. In the remaining cases from five to thirty injections were given. The results in the eight cases reported individually may be rated as excellent, but in some of the remaining twenty cases the response was less satisfactory. I have, therefore, graded these twenty cases in four groups: (1) excellent, two cases; (2) good, five cases; (3) fair, seven cases; and (4) unsatisfactory, six cases. In all of the cases reported individually the results may be considered excellent.

In a consideration of the behavior of lupus erythematosus, particularly the peripheral spread and appearance of new lesions irrespective of the presenting lesions, it seemed desirable to consider only the results designated as excellent and good. In the six unsatisfactory cases are included the two in which one or two injections were given, and those in which there was intolerance to the drug. Obviously the results in this group must be placed on the debit side of the drug in an estimate of its therapeutic value, especially since patients were not treated if a pronounced tendency to dissemination was manifested, as it is well known that such patients are intolerant.

In the entire series of twenty-eight cases excellent results were obtained in ten (35 per cent) and good results in five (18 per cent). For practical purposes it may be said that fully satisfactory symptomatic results were obtained in about half the cases treated. These were, however, in a measure selected, as most cases with a tendency to dissemination were excluded. If all patients as they presented themselves had been treated with krysolgan, the results would not have been so satisfactory. Despite its disadvantages, krysolgan has probably afforded results that could not be duplicated by any other single therapeutic procedure except the use of other gold preparations.

METHOD OF ADMINISTERING  
KRYSGOLGAN

It is apparent that while krysolgan is a valuable therapeutic agent it cannot be considered specific for lupus erythematosus, and various methods of treatment will be necessary in the future as in the past. However, it may be possible, by careful attention to detail, to improve the results of krysolgan still further. In the series there were three cases intolerant to adequate dosage. In one only a single minimal dose could be given. In such a case manifestly no benefit will be obtained from the drug. In the second case eight, and in the third case sixteen, injections could be given. While in neither of these were the doses maximal, it is possible that small doses with long intervals might eventually have secured the desired result. In two cases fully adequate dosage was given (if one may judge from experience) without effect. In the



seven cases in which "fau" improvement was noted, the dose seemingly was adequate but more of the drug might have produced more improvement. Whether a time interval with a second course would show better results is not apparent from this series. It is possible that the individual dose as well as the total dose might have been materially increased advantageously in some of the cases. In that event, the dosage must have been strictly individual without a predetermined method of administration as individual variance in tolerance is pronounced. Further careful study of these points seems desirable.

#### COMMENT

Schamberg and Wright in a recent comprehensive article reviewed the literature with regard to the use of krysolgan in lupus erythematosus, I shall not, therefore, review it here. They used gold and sodium thiosulphate and obtained results similar to those obtained with krysolgan in my series, in about the same number of cases. I hope to be able to report such a comparison in my own experience in a future article, since gold and sodium thiosulphate is being used systematically at The Mayo Clinic. Krysolgan was first used in this series in September, 1926. Minimal doses at long intervals were given in the first six cases. After that the dosage was materially increased and the interval shortened without the occurrence of alarming symptoms. The patients who proved to be intolerant complained of general malaise with aching in the joints and a morbillous eruption. There was no evidence of true dissemination and the eruption

involved spontaneously after the drug was discontinued. One of the patients with an eruption of the chronic disseminate type returned a few months later because of an acute toxic syndrome, the result of acute lupus erythematosus. Sensitiveness varies enormously in different persons and treatment in a given case should be approached with great caution, however, large doses may sometimes be given advantageously. It would seem that the results obtained are reasonably permanent. In this series relapse did not occur in cases in which the response was satisfactory. More time must elapse before opinions on the permanency of results can be given. Some of the patients in this series have been well for about a year and a half. Krysolgan is evidently a remedy of real value in lupus erythematosus, in the chronic type at least it is probably superior to any single drug except some of the other gold preparations.

#### SUMMARY AND CONCLUSIONS

Doses of krysolgan varying considerably in amount and frequency have given satisfactory results in 50 per cent of twenty-eight cases of the chronic type of lupus erythematosus. These results could possibly be improved by careful attention to details as experience with the drug increases.

Patients vary enormously in sensitiveness to the drug but dangerous complications did not develop in this series. In three of the twenty-eight cases a morbillous eruption, general malaise, and pains in the joints developed but there was no evidence of true dissemination. As yet no decisive conclusion can be reached with regard to the permanency of the results.

# The Physician's Dental Education\*

By WILLARD J. STONE, M.D., *Pasadena, California*

A DISCUSSION of problems in which dentists and physicians are mutually interested can only be profitable if consideration is given to those features of their work which will make them more efficient advisors in matters of health. The public generally have advanced in matters of disease prevention quite as rapidly as the facts have been made available for them. Of all the means which have furthered the progress of medical and dental diagnosis the discovery of the X-ray by Roentgen in 1896 should take first place. The greatest advances in the clinical application of this discovery have occurred during the past fifteen years. The attention given by physicians to oral sepsis and its influence upon the health of the individual harboring it was negligible until about 1910 when Dr. Frank Billings published his articles upon focal infections. Since then physicians and dentists have found it necessary to cooperate in their work, to a degree not before considered necessary, in order to secure for their mutual patients the best results obtainable.

I have been impressed for many years with the cursory attention paid by physicians generally to the condition of the mouths of their patients. If some lesion is present of which the patient complains the mouth will be examined, but even then with little understanding of the basic pathology which may be the cause of potential or latent disability. Many physicians are totally unable to distinguish pyorrhea even when it is very evident to the dentist. Physicians generally pay little attention to children's teeth beyond the teething period. Their recognition of the need of orthodontia is rather from the standpoint of aesthetics than from the need of the mechanics of the mouth. If a child is born with an evident deformity such as club-foot, the attempt will be made to correct it. An equally important deformity of the teeth will, perhaps in the majority of instances, go uncorrected. Much has been accomplished in the schools by medical and dental inspection, but the limitation of time, the lack of cooperation on the part of the parents, the failure to recognize the importance of the subject by those in authority, and the obstructive tactics of those who do not wish to acknowledge that certain things in nature may go astray, makes the problem a difficult one.

\*Read before a joint meeting of the Pasadena District Dental Society and the Pasadena Branch of the Los Angeles County Medical Assoc., January 17, 1928.

### THE PHYSICIAN'S DENTAL EDUCATION

Because of the growing appreciation and recognition that dentistry is an important branch of health service and cannot be ignored in the training of general practitioners of medicine, it will be of value to physicians interested in medical and dental education to study the Carnegie Foundation Report upon Dental Education in the United States and Canada, by Dr. William J. Cies, published in 1926.

I have endeavored to obtain data from leading medical schools regarding the amount of instruction given medical students in problems connected with dentistry since every practitioner of medicine should consider oral hygiene and oral disease as important problems in the care of patients. In reply to the inquiry the deans of seven of the leading schools of medicine in this country replied that no systematic instruction was given students of medicine in modern concepts of dentistry. In eight others of the leading medical schools partial instruction was given either in the wards where the clinical clerks had access to the opinion of a supervising dentist or dental internes or unorganized instruction was given in oral hygiene, prophylaxis and disease incidental to the general courses in medicine and surgery. At the University of Minnesota lectures in dentistry are given to senior medical students. At the University of Michigan the interpretation of dental films is taught as part of the course in roentgenology and instruction is given

to senior students in oral hygiene. Washington University gives a required course in stomatology. At the University of Pittsburgh and at the University of Pennsylvania students are taught the interpretation of dental films and the importance of oral hygiene. Dr. Stengel believes that "the whole question of the importance of dental infections is sufficiently taught," or as he expresses it "perhaps a little more than sufficiently."

The fact may be emphasized that such instruction as is given is adequate but that, with few exceptions, because of the overcrowded condition of the curricula in all modern schools of medicine there has developed of necessity, a restriction of special courses due to the lack of time. Of the seventy-nine medical schools in the United States only nine in 1924-25 had required courses in oral hygiene, oral surgery or clinical dentistry in the undergraduate instruction. Many details of the specialties do not properly belong in the undergraduate medical course. With this point of view many educators, notably Dr. Emerson of the Indiana University School of Medicine, are in sympathy while Dr. Edsall of Harvard has expressed the view that a great deal of the difficulty in medical education in recent decades has been due to the constant multiplication of special courses.

Each decade of experience in medical education, in an age of rapid advancement of knowledge, will serve to emphasize those features of instruction which are to be important to

the physician in the care of the sick. It has become necessary for the physician today, perhaps more than at any other period of medical history, to possess facts of practical value. While patients may be interested in a physician's academic propensities, they are much more concerned with his ability to adapt facts which may be of value to them. It has become a matter of what is relatively important and what is relatively unimportant for the physician to know since he cannot know all. The advance of knowledge has made it necessary for the physician to know something of the problem of dentistry in a definite way, for as the family advisor in matters of health he may be the first one to have opportunity to impart the facts.

The Carnegie Foundation survey is comprehensive and will do much for dental education in the future. One of the changes recommended has led to a course of five years consisting of two pre-professional years of college study and an undergraduate curriculum of three years to cover intensive training in oral medicine and clinical dentistry. This plan will leave for post-graduate instruction combined dental and medical courses for the training of specialists in oral surgery, for public health service and for research. Dr. Pritchett in his preface to the report, recognizes the difficulty of professional training and hopes that the problem may be solved in order that "the fruits of modern scientific health service may be within reach of that great majority of mankind that live upon modest incomes, for to train up a generation of physi-

cians, of dentists, of nurses, whose service is so costly as to be out of reach of the self-respecting man of modest means who desires to pay his way, would be a dismal mistake in civilization." He does not venture suggestions as to how this desirable state of affairs may or will be brought about. It is apparent that if medical and dental curricula, as at present designed, could have adequately covered the ground of education in the essentials in a shorter period of years educators would have recognized the fact. It has not been a question of how short a period of instruction the student needed but rather how long a period was necessary to furnish him the proper training. If prolonged training is necessary for physicians and dentists to do the right kind of work it is hoped that the public will find a way to meet the expense necessary for such labor as a health investment. The right kind of dental care can never be done upon the basis of quantity production. One great hope lies in the fact that education of the public as to the proper care of children's teeth will make unnecessary much of the extensive work now required in many adults since a large percentage of all cavities in teeth develop before the age of twenty-five years.

There is need for closer cooperation between dentist and physician, for as Dr. Gies has so aptly expressed it, "despite the prevailing medical lack of information regarding clinical dentistry many physicians often against the dentists' protests peremptorily order extraction of particular teeth or sometimes of all remaining

teeth, on the assumption apparently that a dentist's judgment cannot be right when it conflicts with a physician's guess." He also mentions the fact that "the biological ignorance of many dentists owing to deficient education in the medical sciences and in the requirements of oral medicine, often accounts for the disrespect of physicians for the dentist's point of view and frequently makes dental consultations concerning the health of patients unreliable." The conclusions reached may be summarized as follows: "(1) Dentistry should no longer be ignored in medical schools, (2) The proper care of the mouth is as significant for the maintenance of health as any of the accredited specialties of medical practice, and (3) When dentistry becomes equivalent to an oral specialty of medicine it may be expected to bring many dental maladies into the realm of completely preventable disorders."

The prevention of disease and disability at all ages should become the predominating motive in the work of physicians and dentists

#### PYORRHEA

Our understanding of the character of the progressive destructive process known as pyorrhea, as well as periapical lesions, has been much clarified during the past decade. So far as pyorrhea is concerned it seems that investigators have gone about as far as is necessary or expedient in the endeavor to find specific bacterial causes for the condition. So far as I am aware no definite organisms, vegetable or protozoan, may be held directly responsible for the condition

in its incipency. While the oral cavity always contains bacteria, most of the organisms which may be isolated from it are harmless saprophytes. Some varieties may undoubtedly become pathogenic under certain conditions. Steinberg discovered the diplococcus of pneumonia in healthy sputum.

A great many mouths harbor organisms which may be inert so far as their host is concerned. This carrier state may be a potential or actual source of danger depending upon a great many factors of immunity, specific as well as non-specific, the nature of which are unknown. That, however, the bacteria present in the mouth may be directly responsible for pyorrhea still requires proof. Indirectly as invaders of gum tissue surrounding healthy teeth bacteria probably play an important though secondary rôle. In a mouth neglected as to ordinary cleanliness in which caries and malocclusion with retention pockets exist, it is probable that tissue destruction is hastened by the bacteria present, but the primary cause lies in the lack of care and the mechanical features of malocclusion which make proper mastication difficult, if not impossible. Pyorrhea may be regarded as a slow progressive retrograde involvement of first the gingiva and later, during the course of years, the deeper tissues surrounding and supporting the teeth. The insidious nature of its progression may be taken as its most important characteristic.

In all essential tissues degenerative processes occur slowly with the course of years. Muscles become atrophic

or fibrotic from lack of proper use, the bones become decalcified, while the aorta and smaller arteries become sclerotic as a natural result of wear and tear favored many times by disease in other organs, or by abuse. From this standpoint the progressive lesions of pyorrhea may be looked upon as a degenerative condition rather than disease. Relatively few individuals beyond the fourth decade of life escape it. Relatively few physicians until a decade ago were interested in mouth sepsis. They preferred to leave the problem to the dentist, who many times failed either because of lack of knowledge, because of indifference, or through failure to impress upon the patient the importance of securing a clean mouth.

#### PERIAPICAL AND RESIDUAL INFECTION

From every point of view it is desirable to possess a mouth free from pulpless teeth. For that large percentage of the population who have pulpless teeth with the corresponding tissue changes associated with them, the problem of treatment requires the best cooperation between dentist and physician. We may consider immediate and remote effects of acute or chronic periapical infection. In the acute abscess developing about the apex of a pulpless tooth with symptoms localized to the area involved, it is beyond the province of the physician to determine the most suitable local treatment advisable. Drainage alone may be the wisest procedure at this stage, but this the dentist must decide. For an acute abscess with focal symptoms, such as iritis, extraction may be the wisest procedure and the responsibility should be divided

between the dentist and physician. Little difficulty is experienced as a rule in deciding the line of action in such cases for the pain may be acute and attention is focused upon its relief.

In chronic periapical infections it is safe to say that a very large majority may present no symptoms by which the attention of the patient is called to their presence. A large number of patients present themselves each year to physicians with the remote effects of such foci of infection. The physician depending upon his habit of thoroughness, or the lack of it, may fail to consider other foci of infection which such patients may harbour and without consultation with the dentist advise extraction, with the promise that arthritis or neuritis symptoms will be promptly relieved. Such advice may be detrimental to the patient as well as react against the physician. It is not within the physician's province to decide alone upon such matters. It is his duty to study so far as possible all foci of chronic infection which may be harmful to patients. This involves a consideration of the tonsils and sinuses, the digestive tract and its appendages, as well as the prostate, the seminal vesicles, the cervical canal, the middle ear, as well as such conditions as bronchiectasis, pyelitis or pyelonephrosis. The problem is a large one.

So far as the teeth are concerned physicians should realize that the dental roentgenogram does not tell all of the story. The mistake may be made in advising that pulpless teeth should be saved which do not show evidence of infection on the X-ray film. The work of Rosenow, Haden

and many others who have studied the problem should be carefully considered. The literature has grown enormously during the past decade. Price, Haden, Moody, Rickert, Beckwith, Simonton, Meisser, Gardner and others have added much to existing knowledge of the subject in the past few years. The following facts may be taken as established, (1) That the periapical tissues about teeth which give positive roentgenogram evidence of infection contain streptococci, usually of the non-hemolytic variety. The common varieties, by carbohydrate fermentation tests, have been found to belong to the groups known as mitis, fecalis and salivarius. Haden's recent work may be summarized as follows: cultures were taken from the apices and periapical tissues surrounding teeth removed "without contamination", in one series of 500 pulpless teeth which gave radiographic evidence of infection. The percentage of positive cultures was 70.4% in glucose-brain-broth-agar, and 91% in glucose-brain broth. (2) Pulpless teeth which showed negative radiographic evidences of infection likewise gave a high percentage of positive cultures, i. e., in 600 such teeth the cultures were positive in 55.9% on glucose-brain-broth-agar and 83.8% in glucose brain-broth. Haden found streptococci only in 806 of 890 pulpless teeth (90.5%), while streptococci and staphylococci or staphylococci alone were found in 12 of 890 pulpless teeth. These findings are higher than those of Rickert who obtained positive cultures in 51% of 200 pulpless teeth. (3) From the experimental work of Rosenow, Haden and

others, it has been shown that a variety of conditions have been produced in animals by cultures obtained from foci of infection about the teeth of patients. These conditions corresponded more or less accurately to the lesions present in the patients. Such selective localization has been repeatedly demonstrated for chronic arthritis, myositis, iritis, duodenal ulcer and pyelo-nephritis, less frequently encephalitis and thyroiditis have been produced. It may be mentioned that cultures from pulpless teeth, negative by roentgenogram, produced in 232 rabbits, a total of 168 lesions of joint, kidney, muscle, endocardium, myocardium, brain, eye, stomach and duodenum. The cultures obtained from pulpless teeth with positive roentgenogram evidence of infection produced in 224 animals a total of 181 lesions (Haden).

#### DISCUSSION

There has been a tendency to two extremes in the consideration of selective localization of infection from infected teeth. One group has believed that all foci of infection were inimical to health, while the other group has believed that the matter has not been proven because first, the methods used were not believed to be comparable to those which obtain in man and second, because some workers have failed to corroborate the work of Rosenow, Haden and Price. It must be acknowledged that some workers who have been adverse in their criticism, have not followed the original technic in their endeavor to prove the question of selective localization. Those physicians and dentists who believe the question still in

a debatable stage take the position, not without some logic, that bacteria such as streptococci exist in the tonsillar crypts as well as in the nasopharynx and bronchial secretions of a large proportion of individuals, and yet such individuals may manifest no evidence of disease as a result of the presence of such bacteria.

The question cannot be decided quite so easily as this argument would imply. Periapical or residual infection exists as a more or less deeply entrenched focus in bone where adequate drainage is practically impossible. Some dentists have taken the position that, given evidence of such infection, there has been brought forth no proof that such foci are capable of producing systemic disease, in other words they believe that in many instances such foci are so-called sterile abscesses or are manifest evidences of healed bone changes. Such believers have deplored what they have termed unscientific proof founded upon speculation, and have continued to advocate retention of such teeth by any method of temporizing treatment which happened to be in vogue. I frequently see new dental appliances attached to teeth with obviously diseased roots and surrounded by pyorrheal abscesses, and not infrequently has expensive, extensive and tedious root canal filling been done in teeth with definite apical disease. Dentists who sanction such work justify their position because of the occasional rare instance, *from roentgenogram evidence alone*, that healing of the diseased apical tissue may take place. Their attention should again be called to the fact that

the percentage of positive cultures capable of producing definite pathologic lesions in animals, from pulpless teeth with negative roentgenographic evidence of infection, is nearly as high as that obtained by cultures from pulpless teeth with positive roentgenographic evidence of damage. It may be observed at this point that the conditions under which animals are injected intravenously with relatively large cultures of bacteria from infected teeth do not in all probability occur in man. Septicemia does occasionally occur from an area of infection about the teeth, but that it is a common occurrence must be doubted. The experimental side of focal infections about the teeth would be much clarified and the experimental workers would much more definitely establish their position, if they were able to produce in animals conditions similar to those which occur in man, that is, to embed their cultures in the animals teeth and demonstrate subsequently the pathological lesions found in man. It is possible that such proof may be obtained in the future.

There is reason to believe in the majority of cases that chronic foci of infection about the teeth produce their damage to health through slow absorption of toxins. In any large series of cases there will be a few in which the evidence may point to hematogenous transportation of the infection itself, but in the large majority the evidence points to slow absorption of toxins as the cause of certain symptoms such as myositis, neuritis or arthritis.

It may be appropriate at this point to quote from an address by Lewellys



F Barker before the Maryland State Dental Association at its annual meeting in 1926. He stated (1) "that patients exhibiting various conditions (such as arthritis, myositis, neuritis, endocarditis, uinitis, secondary anemias, etc.) do not always carry demonstrable primary foci of infection, (2) that when focal infections are present certain causal factors often cooperate with them in producing the conditions, and (3) that, owing to the lamentable tendency in this country to push ideas and practices to extremes there has, during the past five years especially, been clear evidence of over-emphasis upon the importance of focal infections as a cause of both local and general bodily disorders."

The position of the physician in the consideration of the conditions mentioned above is difficult, since in different individuals there may be different etiological factors. The patient with persistent myositis or neuritis may have periapical disease but he may likewise have a disturbance of metabolism with the retention of abnormal amounts of nitrogen products in his blood which in turn may be due to organic kidney disease or may be functional in the sense of faulty oxidation in an individual who exercises too little and whose intake of proteins is excessive, or again whose ability to utilize proteins may be lessened by hypothyroid activity. In those diseases which have a single etiological cause such as syphilis, typhoid fever, diphtheria, tuberculosis and scarlet fever, the clinical course follows a more or less orderly sequence. Complications which alter the regular

X may be due to infections which

while present in many individuals in health, are increased in virulence under certain conditions. Thus during the World War it was a common experience in the Base Hospitals to find that many soldiers were throat carriers of streptococci. No apparent harm came to many of them as a result of such carrier state. But when such individuals developed pneumococcus pneumonia they suffered from various complications such as empyema or otitis media which were due to the streptococcus infection they harbored in health. The streptococcus infection under such conditions became exalted in virulence during the course of the pneumonia. Cummings has recently studied the cause of death in small pox and concluded that "small pox is fatal only to throat carriers of hemolytic streptococci." It is apparent then that in the consideration of foci of infection within the body the physician must consider a large number of possibilities, some of which are known but many of which are unknown. It is necessary to consider the welfare of the patient as a whole, and to endeavor to do the most obvious things first. In chronic disabilities if the patient is able physically to undergo the ordeal, the physician should advise the extensive work many times necessary to render the mouth clean. This refers to the elimination of the diseased tissue and pyorrheal pockets by surgery in the hands of those of competent and extensive experience. I realize that I am treading upon somewhat dangerous ground since among the members of the dental pro-

fession there exists no unanimity of opinion on the subject

I have followed the advocates of less radical methods in the treatment of pyorrhea for many years. There are many who believe that the teeth can be *cleaned* by so-called scaling methods. This I believe to be true, but I do not believe that pyorrheal pockets can be eliminated by any method short of surgical resection of the affected tissue. By this method reinfection of the pockets is prevented by the new tissue proliferation which occurs. Otherwise reinfection is inevitable. Such methods are available but are advocated by relatively few dentists largely, I believe, because they are unfamiliar with the results obtained by competent specialists in this field of work. It appears to me necessary to adopt radical means, if the measures may be called radical, to secure the desired end.

If the physician believes his patients' general health will be improved by extraction of pulpless teeth, he should endeavor to influence his patient to submit to such extraction, providing he may secure the assistance of a dental colleague who takes into account the subsequent mouth disability which may follow extraction, and its effect upon the general health of the patient including his digestive capabilities. On the whole nature displays wonderful adaptive capabilities. We are many times astonished at her many ways of compensation for defects. For example some patients for years will manifest no serious change in their general health who have been entirely without teeth and who have coincidentally had achylia.

There are certain risks entailed in any procedure, and it is necessary to consider whether it may not be safer not to disturb what may be a quiescent focal condition. This may be especially true in those who have evidences of extensive damage elsewhere, especially cardiovascular-renal disease. To expect any marked amelioration of symptoms or change in the function of organs the seat of degenerative processes is many times futile. It becomes for the dentist and physician alike in such cases a matter of doing as much as possible to restore adequate function. It may not be a matter of discretion to attempt more.

In the consideration of the extensive work many times necessary one can sympathize with both dentist and patient. Many may choose to take the position that part of a loaf is better than none at all, and are willing to temporize with any kind of work which is easily installed. Few individuals relatively are willing to undertake the expensive overhauling which their mouths demand from the standpoint of modern dentistry. Patients are many times compelled from economic reasons to secure work of a temporary but ultimately very expensive character. They have chosen amalgam fillings because of cheapness which may have been permissible providing the dentist had taken pains to explain that, because of the tendency to decay beneath such fillings within three years in a very high percentage of cases, such work was liable to prove more expensive in the long run.

It is probably true that prior to 1915 ninety percent of the dentistry done *did not take into account care-*

fully constructed restorations of carious teeth in the sense of their relation to the occlusal surfaces of adjacent or opponent teeth. This means that faulty dentistry before 1915 was responsible for much of the work which the dentist with modern training is endeavoring to correct.

Dental education will do much to remedy many of these conditions. Physicians of the coming generations will be given instruction in oral hygiene, more and more emphasis will be placed upon those factors which ultimately produce extensive damage such as malocclusion, more consideration will be given to inspection of teeth of school children, and more education will convince the large ma-

jority of intelligent people, that purely from the standpoint of prevention of subsequent trouble, it is necessary to secure competent advice early in life before extensive damage has been done. It would be a great step forward if dental dispensaries were available in each large community, founded upon adequate endowments by generously inclined people, where those who have an interest in health might secure a competent dental survey with advice covering their particular problems through the years to follow. The large life insurance companies could greatly assist in the matter of health education through publication of the facts. It would remain for those who believe to follow the advice given.

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# Hypothyroidism\*

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THE symptoms produced by excess of thyroid secretion or of aberrant thyroid secretion are so striking, and the explanations of the pathological-physiology have been so varied, that an enormous literature has accumulated dealing with hyperthyroidism. The opposite condition, lack of thyroid secretion (hypothyroidism), has been relatively neglected by the debaters and investigators. It is probably not because of the difference in the incidence of the two disorders of the gland, but rather that attention has been almost exclusively directed to the more obvious of the two and the one which actually is the more serious in its effects upon the life of the affected individual. Hyperthyroidism if left alone causes disability and often death. Hypothyroidism if left alone at the most causes disability only, but most often causes merely a marked slowing of the affected person's activities.

The thyroid gland is not absolutely necessary for life. It can be and has been removed with consequences serious enough to the individual, but not fatal. The hormone, now known universally as thyroxin, is absolutely necessary for normal cellular activity, for growth, for sexual and mental

development. The action and interaction of thyroxin upon the other endocrine glands need not be gone into here. I take it for granted that these relationships are known to all. Our interest lies in the bizarre effects of an insufficient amount of thyroxin produced in the gland upon the bodily functions. Between the total lack of thyroxin and the normal amount lie a great number of states of lessened amount. Were this the only factor the problem would be fairly simple. It is complicated by the fact that every individual is different from every other individual, his response to irritants or to lack of any one important internal secretion is of different degree not only among individuals but in the same individual under varying conditions of nutrition, climate, infection, mental state, and what not. Consequently no mathematical measurement can correlate symptoms, no matter how accurate the instrument or apparatus may be.

For convenience of description hypothyroidism may be divided into three groups (1) Cretinism, (2) Myxedema of adults, (3) Masked or Occult Hypothyroidism. We are concerned here only with the last group. Theodore Kocher in 1909 was the first to call attention to slight forms of thyroid insufficiency. Previous to

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that time attention had been focused on cretinism and myxedema and the brilliant therapeutic results of Horsley and Murray. Apparently it was not thought that there might be symptoms resulting from continuous secretion of less than the normal amount of the thyroid hormone. Magnus-Levy in 1897 had found that there was decreased metabolism in severe hypothyroidism. Such estimations were only possible in well-equipped laboratories. To Benedict, du Bois and their associates we owe the practical application of the old cumbersome measurements of body metabolism. The development of the apparatus for measuring the basal metabolism has enabled us to pick out cases of masked hypothyroidism from other somewhat similar symptom groups. The condition is common. It occurs all over the world and is not confined to areas where goitre is endemic. However, in localities where simple goitre is common one would expect to find increased incidence of hypothyroidism in the adult population. No statistics are available yet on this question.

Endemic simple goitre is considered to be in itself an expression of a lack of some substance (iodin) which the gland must have in order for it to elaborate its hormone. If this substance is not supplied in sufficient quantity a lack of hormone results. Whether this lack will show in any particular individual later in life depends on his inherited constitution and upon various stresses and strains from his environment. If there is a lack of the thyroid hormone there is greater susceptibility to infections of various kinds, for the hormone has a

decided influence upon bodily resistance and upon antibody production.

It behooves us, as doctors who are interested in restoring health to our patients, to pay more attention to the hypothyroid states.

I have taken from my records twenty-five consecutive cases, twenty one females and four males. This is about the usual proportion. The youngest was a girl twenty-one years old, the oldest a woman of fifty-six. Thirteen were over forty years.

*Heredity*—No data were obtainable concerning the influence of heredity. Barrett (1), among others, is convinced of the importance of heredity. He reports a remarkable family traced by him through six generations. Of sixty-one members hypothyroidism with dystrophies of the nails and hair were present in fourteen. There was also high frequency of feeble-mindedness and of neurological disorders of degenerate type. I have considered the following possibility. The Great Lakes region is known to be a locality in which simple goitre is common and where analyses of drinking water show almost total lack of iodine. The country was settled by people from the Atlantic Coast. After two or three generations with little or no iodine supplied in the diet, should it not be expected that the present generation would show more or less result of the lack of iodine and be otherwise well? Surveys show that from seventy-five to eighty-five per cent of young women have enlargements of the thyroid gland. This can only mean that iodine is lacking. Following pregnancies and other strains upon

the gland they arrive at middle life with so little thyroid hormone that it is not sufficient to carry them as normal people. I have no statistics to prove this hypothesis but am at present seeking to gather some. I present it as a working hypothesis to explain the frequency of the condition.

*Etiology*—It appears that not enough attention has been paid to injuries of the thyroid gland in infectious diseases (2). Attention was called by Kocher to mild states of hypothyroidism following severe general infections, typhoid fever, influenza, dysentery, furunculosis. Neither tuberculosis nor syphilis seems to play much part in producing hypothyroidism. Janney (3) feels that trauma and surgical operations are of little importance in etiology. The two periods of a woman's life, the beginning and cessation of menstruation, are important factors. Operations in which the ovaries are totally or almost totally removed also are influencing conditions.

Lawrence (4) studied twenty-five cases and found in 11 patients' minds the immediate cause was, 5 who said it followed pneumonia or severe influenza, 3 who attributed their trouble to pregnancy with toxemic symptoms, 2 thought that severe nervous and physical strain caused their trouble and 1 followed an operation for goitre. In only two of my cases was there a reasonably certain connection between infection and onset. One was a young man 22 years old who when 15 years old had severe influenza and pneumonia. The other was a young woman of the same age

who when 16 years old had peritonitis following an operation.

*Symptomatology*—An unusually bizarre symptomatology is characteristic of this class of patients. Usually they are not ill. They go about their business, hold positions of more or less responsibility and often exhibit considerable energy. They come to the physician principally on account of an undue fatigability. Even those with apparent energy do their daily tasks, then are so exhausted that they want to go to bed as soon as the evening meal is over. All writers have noted this as the most important single symptom. It was the chief symptom in 18 of my 25 cases and was present in all. "Tired out all the time," "Feel all in," "Can't go out to dances because I am so tired at night," are some of the expressions used. Constipation is common, a simple sluggishness of the bowels. McCarrison (5) has called attention to intestinal stasis in hypothyroidism. One of my patients retained a barium meal for 56 hours. This has been frequently noted by all writers and T. R. Brown (6) has again called particular attention to this condition in women over forty.

Headache and rheumatic pains were the chief complaints in four cases. We are so obsessed with the idea that focal infection is at the bottom of such cases that perfectly good teeth are extracted, perfectly innocuous tonsils removed, sinuses operated upon and drained, and appendices, even gall bladders, removed in the effort to relieve these people.

A colleague in the middle forties had had for several years repeated attacks of back and joint pain and stiffness often completely incapacitating him. He had noticed for several years past that he had difficulty in keeping his weight down and that he was losing his "pep," as he expressed it. He had had his tonsils removed, several teeth extracted and was about to have other "suspicious" teeth extracted when it was suggested that before he lost all his good teeth he might have a basal metabolism test made. Physical examination revealed no abnormalities and X-ray films of various joints and of the spine showed no lesions. His rate was minus 13 per cent. Not very low, one might say. However, as I believe that a small minus rate has a far greater significance than a moderate increased rate, I recommended that he take thyroid extract. He began with six grains daily. Within a week he was feeling much better. His stiffness disappeared. He has found that five grains daily is his dose. When he takes four grains for a few days his stiffness and pain return. When he takes six grains he finds he becomes a bit jumpy and sleeps badly.

Sundry aches and pains are complained of. Five patients had abdominal pain, the kind of pain which has been so often called chronic appendicitis, in general a meaningless diagnosis, and for which so many have been operated upon, gaining no relief whatever. One patient, a young woman, had cramp-like pains over the heart which disappeared rapidly in treatment.

Irregular menstruation was present in only two patients. One might expect more menstrual disturbances. In one case there was partial infantilism, a girl of 22 who had never menstruated and who looked and talked like a child of eleven years old. Two complained especially of drowsiness. It was hard to keep awake. One of these was a woman of 36 who was beginning to be myxedemic, the other was a slender man of 50, a priest.

Many complained of susceptibility to cold. No one complained of dry skin or of thinning of the hair or coarseness of the hair. These were occasionally elicited by questioning. Lawrence (7) notes this also. No one complained of the lack of perspiration on exertion although several admitted that that was true when they were asked about it.

Several complained that they had great difficulty in keeping their weight within reasonable bounds, others complained that however much they ate they could not put an ounce of weight on their spare frames. Hypothyroidism is certainly not a concomitant of excess weight any more than it is of under weight. This should be emphasized as the impression seems to be current that one does not find hypothyroidism in thin, underweight people. One of my patients definitely complained of losing weight.

*Physical Signs*—The general physical examination of these patients usually reveals very little. Some are overweight, some are underweight, some are normal weight. The thyroid gland may be visible as a swelling at the root of the neck or there may be



no evidence of the gland on inspection. So far as known there is no one type of bodily structure which seems particularly prone to develop lack of thyroid secretion.

The pulse rate and the blood pressure show no uniform decrease such as have been thought to be the case. In my series the lowest pulse rate was 56, the lowest blood pressure 90/70. The highest pulse rate was 104, the highest blood pressure 150/80. Higgins (8) says that the pulse may be accelerated, loss of weight occur and the condition not differ materially from the early active syndrome. Lawrence (9) says "A normal or accelerated pulse rate does not preclude a coexisting hypometabolism due to thyroid failure." Studying the effect of thyroid extract upon the heart he thinks that there are two effects, one is increase in work, the other is improvement in nutrition. The first often precedes the second by some time.

The blood shows no specific changes. Greene and the writer (10) reported upon a chlorotic type of anemia in young women with hypothyroidism. Mackenzie (11) reported secondary anemia and Stone (12) recently reported cases of myxedema which had masqueraded under the guise of pernicious anemia. Dock has also noted this type of anemia. There was no chlorotic type of anemia in the series here reported. Anemia was not the usual condition. When it occurred it was secondary anemia.

Kocher in his original description of the mild states of hypothyroidism bore heavily upon a relative lymphocytosis to substantiate the diagnosis.

Even this is not always present. Lymphocyte cells, large and small, ranged from 47 per cent to 24 per cent. The former had BMR of minus 19 per cent, the latter of minus 16 per cent. One patient, a woman of 34, 5 feet 7½ inches tall, weight 122½ pounds with a pulse of 68, blood pressure of 100/80 had 4,800,000 red cells, 95 per cent hemoglobin, 7000 white cells with 30 per cent of lymphocytes (24 per cent small, 6 per cent large). The basal metabolism was minus 22 per cent.

The basal metabolism rates in this series were between minus 12 per cent and minus 30 per cent. These estimations were all made with the Benedict-Roth machine using the graphic method and were made by the same person, a physician thoroughly acquainted with all the vagaries of making the readings. All patients were under standard basal conditions. Only those cases were taken whose metabolism was below minus 10. However, my conviction is that with symptoms such as have been described above even a consistent minus 8 per cent (allowing for errors which may creep in) may mean hypothyroidism. The significance of a small minus value is much greater than that of a moderate plus value. It is easy to overventilate and raise the consumption of oxygen with a corresponding increased metabolic rate. It is not easy, under the conditions of the test, for the patient to underventilate and produce a minus rate. Plus rates to me have no particular diagnostic meaning unless symptoms and physical signs agree with the reading. The minus reading, on the contrary, has

weight even though symptoms are indefinite and slight. Undoubtedly many patients live their lives through with a slight decrease in thyroid hormone and are never aware of the fact. Cushing (13) believes that many unrecognized hypopituitary cases are all around us. Some of these hypopituitary cases show a decreased metabolic rate. However, with the known interrelationship between the thyroid and the pituitary and the known influence upon cell metabolism of the thyroid hormone, it would be difficult to say whether such decreased metabolic rates were not due to the lack of thyroxin rather than to the lack of the hormone of the posterior pituitary lobe.

There is no relationship between the number or severity of the symptoms of which the patients complain and the depression of the metabolism. My experience coincides with that of Lawrence (14) who says that there is no relationship between the depressed metabolism and the amount of thyroid extract which will bring it to normal. Every case is a law unto itself and only experiment can fix the proper amount of thyroid extract required.

Lawrence (15) has found metabolic rates between minus 15 and minus 30 in cases of pathological fatigue (whatever that means), in cases of syphilis of the central nervous system, in cases of nitrogen starvation and in cases of hypofunction of the endocrine glands.

*Diagnosis*—It is not difficult to make the diagnosis of these cases if one is on the lookout for the condi-

tion and has the basal metabolism taken by a competent person. The methods of laboratory examinations in vogue now in so many places are not such as to inspire confidence in the results. Too many times the basal metabolism apparatus is turned over to a young woman technician who has learned to run the machine. Reports of plus 8 may well be actually minus 14 or less. With this comment in mind, the fact remains that the basal metabolism is the crucial test in the diagnosis.

In an otherwise rather normal looking person, a friend whom one sees frequently, complaints of being tired, of being a bit constipated, of having vague rheumatic pains or of vague abdominal pains do not necessarily suggest the possibility that he, or particularly she, may be one lacking in thyroid hormone. Yet such may be the case.

One must not be misled by the length of time the symptoms have been present. In Lawrence's (16) cases the average duration was 8 years. It was not possible to place the onset in all of my cases. One case followed measles and scarlet fever at the age of 8, twelve years before I saw her. One case seemed definitely to have followed a pregnancy 8 years before she came for examination on account of drowsiness, gain in weight, slight loss of memory but particularly because she became tired so easily.

A rapid pulse rate does not preclude hypothyroidism. All writers speak of this occasional paradox. Fever also may occur. Lee (17) has recorded a case with fever of weeks standing

from 99°-100° F, which had pulse rate of 50-66

*Differential Diagnosis*—Many cases are called neurasthenia, nervous exhaustion, etc. I can recall vividly cases seen years ago where the most careful examination failed to discover any physical defect, which I feel now very probably were hypothyroids. Such a case as the following in the present series: a young woman, art student, age 22, came complaining of being tired all the time. While she attended her classes and also taught, she had to drive herself, and by evening was utterly exhausted. She had been to a number of doctors, several of whom looking at her apparent health and well nourished body, scarcely examined her but told her she was nervous. She should go ahead and forget it. By the time she came to me she was disgusted with doctors but had consented to "go once more" as she said. She was averse to telling her symptoms as she had been laughed at frequently on account of the apparent triviality of them. A symptom which she had newly developed was a gripping pain in the upper left chest, so severe that when it came on she could scarcely breathe. In her past history there was dilatation and curettement of the cervix for vaginal discharge when she was fourteen years old. An appendix operation followed by prolonged infection, ventral hernia and repair of hernia at 18 years. Also she said that she gained weight so quickly that she had almost to starve herself in order not to grow enormous. Physical examination revealed no organic lesions. The

thyroid region seemed a little full but there was considerable fatty tissue in the skin. The BMR was minus 16. She was given thyroid extract. The next BMR eight weeks later was zero and she was feeling quite well, not only able to work without fatigue but she could eat without gaining weight rapidly.

There are cases which for want of a better diagnosis one has called gastro-intestinal intoxication or even migraine. In 1922 a thin woman, small boned, and of small frame, then forty-one years old, complained of recurring attacks of headaches and nausea. Her father suffered from headaches all his life. He died at 86 years old, the cause not known. One sister has headaches and one brother had pulmonary tuberculosis. When twenty-eight years old she weighed 135 pounds. About that time she had an attack of jaundice followed by stomach trouble. She has never been well since. Her weight gradually was reduced to 109 pounds, she was constipated and had frequent headaches oftentimes with nausea and vomiting. The most careful physical examination including gastro-intestinal X-ray examination failed to show any lesions. There was general abdominal soreness on palpation, a sign the significance of which was not appreciated at that time. She was given general supportive treatment, gained four pounds in three months but was not much improved. She was next seen in February 1926 in about the same condition. She was quite constipated and the skin had a muddy, somewhat yellowish tint. No gall bladder or liver disease

could be demonstrated. When she was next seen in April 1928 she had the same series of symptoms. This time the diagnosis of hypothyroidism was made and she was given a B M R test. It was minus 20. Thyroid extract was given. At present writing she is better, has gained weight and her bowels move more normally.

General soreness in the abdomen on palpation, particularly in the appendix region, is frequently found. Chronic appendicitis has been a diagnosis often made and many a normal appendix has been removed without benefiting the patient. In the common acceptance of the term I do not believe there is such a disease. Subacute and recurrent appendicitis is a definite entity and operation is a curative procedure. But that an appendix should become chronically diseased and give indefinite symptoms without previous acute attack is, I believe, a rare occurrence. The art student reported above had "chronic appendicitis," was operated upon and then developed peritonitis and later ventral hernia. This was in my opinion an unjustifiable operation.

Others as well as I (18) have reported upon the vague gastro-intestinal symptoms of occult and early tuberculosis of the lungs. Such cases have been operated upon both for "chronic appendicitis" and for gastric ulcer.

Occult tuberculosis can readily be confused with hypothyroidism in the underweight individual. I am sure now that I have made this error in the past. The symptoms are practically identical. The chief symptom is undue fatigability and a train of

symptoms which are called neurasthenic. The basal metabolic rate settles the diagnosis, for in afebrile tuberculosis unless the patient is markedly undernourished the B M R is normal (19). The following case I feel sure I should have diagnosed occult tuberculosis several years ago.

A priest aged 49 said that up to two years ago he had never been ill. He fell on the ice at that time striking his back, and since he had not been altogether well. He is tired all the time and has a tendency to fall asleep as soon as he eats his evening meal. He has not lost weight, has a good appetite, but is constipated. There has been some difficulty in starting his urine. A year ago he had his prostate massaged. There was no cough or shortness of breath. On examination he was a fairly well nourished man, 5 feet 6 inches, weight 142 pounds. There was slight impairment of the percussion note at the right apex posteriorly. The breath sounds were harsh, but no râles were heard. The lungs were elsewhere clear. The heart was normal. The pulse rate lying down was 80, the blood pressure 120/80. Nothing abnormal was felt in the abdomen. The reflexes were present. The blood showed no abnormalities. The prostate gland was enlarged and soft. The urine was normal.

Fluoroscopic examination of the chest showed slightly hazy apices, both lighting up on cough, greatly enlarged hilum shadows with heavy streaking in the inner zones in the 1st and 2nd interspaces on both sides. The right diaphragm was slightly tented at its middle portion. The heart shadow

was normal Intradermal O T 1/10 mg was strongly positive in 24 hours. The basal metabolic rate was minus 17 per cent.

*Treatment*—Either thyroxin or thyroid extract can be given The former given intravenously may be used where one wishes a rapid effect. However, I have not found it necessary to use thyroxin and prefer the tablets of thyroid extract given by mouth Dosage varies widely Some patients have taken fifteen grains daily Six to nine grains daily is an average dose There is no relationship between the depression of basal metabolism and the amount of thyroid which will normalize the patient Lawrence (20) says that in thyroid deficiency thyroid extract tends to normalize functions, to bring low pressure up and high pressure down and can benefit symptoms only in so far as it can normalize the nutritional level of the body

In one of his papers he draws one conclusion which cannot be too strongly emphasized He says "thyroid extract in non-toxic amounts has no specific action in reducing body weight, except as it dissipates myxedemic deposits and causes the elimination of abnormal accumulations of fluid By its effect on nutrition it frequently causes a gain in weight as basal metabolism becomes normal Progressive loss of body weight as a result of

its administration is, as a rule, a toxic effect. Its use as an aid in reducing weight in patients with normal thyroid function is therefore illogical, and either inefficient or dangerous"

#### SUMMARY

Hypothyroid states are common and often are unrecognized for years The affected persons in the meantime have a bizarre group of complaints the chief of which are (1) a sensation of being always tired, (2) constipation, (3) susceptibility to cold, (4) various aches and pains, (5) in women, amenorrhea or menorrhagia

Physical signs are singularly lacking Both overweight and underweight are found General abdominal soreness, often greatest in the right iliac fossa, is frequent A carefully measured basal metabolic rate reveals depression in all cases This is the necessary criterion for diagnosis

Differential diagnosis must be made from (1) the neurasthenic syndrome, (2) so-called "chronic appendicitis," (3) migrainous headaches, (4) rheumatic aches and pains now so widely believed to be due and often are due, to focal infection, (5) occult tuberculosis, (6) diabetes, (7) pernicious anemia, etc

Thyroid extract can only normalize the nutritional needs of the body and should never be administered to reduce weight in individuals with normal thyroid function

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# The Causes of Flatulence

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THE symptom, flatulence, indicates the presence of excess gas in the bowel, or the passage of gas from the rectum in noticeable quantities. The causes are so numerous that flatulence is in itself of little diagnostic importance, but occasionally it is the chief or only symptom, or the earliest noticeable symptom, and then its study becomes of value.

From a circumspective point of view gas gets into the bowel in three ways. It may be *swallowed*, may be *generated* in the alimentary tract, or may be *excreted* through the bowel wall into the lumen.

## OUTLINE OF CAUSES

### *Swallowed Gas*

- in the form of gaseous foods
- because of frequent swallowing
  - on an emotional basis
  - with lachrymation in eye diseases
  - with nasal disease
  - with pharyngeal disease
  - with oral disease
  - with esophageal disease
  - from chemical irritation
  - from mechanical irritation
- because of excessive motility of the alimentary tract
- because of decreased absorption in the alimentary tract

### *Gas generated in the alimentary tract*

- from diseased bowel wall
- from foods
  - because of the inherent food qualities

- because of faulty digestive juices
- because of poor absorptive capacity
- because of too rapid passage of food
  - through the small intestine
  - through the large intestine
- because of delayed passage
  - through the small intestine
  - through the large intestine

### *Gas excreted from the blood into the bowel lumen*

- because of saturation of the blood
  - from inhalation of gases
  - from extensive diseased regions in the body
  - from improperly functioning excretory organs
    - vicariously in extensive lung lesions
    - vicariously with severe liver lesions
    - vicariously in advanced renal lesions

## SWALLOWED GAS

Gas is swallowed with every bit of food or liquid that passes down the esophagus, but ordinarily it is in small quantities except perhaps when large amounts of gaseous drinks such as charged water are imbibed. It is removed by chemical action in the bowel lumen, or by absorption into the blood stream. Nitrogen is chemically somewhat inert, and while a portion is undoubtedly absorbed, when ingested in sufficient quantities some may pass on through and become flatus. However, in a healthy individual the probability of flatulence from swallowed air is remote.

Air swallowers as a rule are *not* healthy individuals. There may be a nervous basis for the habit, such as some emotional state. The concomitant flatulence is due not so much to the excess air swallowed as to gas accumulating in the large bowel because of generally increased activity of the autonomic nervous system. In emotional people food is hurried through the stomach and small intestine before digestion is complete, and the undigested unabsorbed food is broken down by colonic bacteria with the generation of gas. The gas is frequently expelled because of restlessness of the large bowel. This will be discussed in detail later.

Air swallowing is apt to occur with focal disease of the upper respiratory and alimentary passages. The irritation produced by pressure from an esophageal diverticulum, an aneurysm, goitre or enlarged thymus may cause it. A small esophageal ulcer or erosion, or beginning carcinoma can make the patient swallow more than usual. The irritation may be from retropharyngeal tuberculous processes, or from neoplasms at the vocal cords, or tuberculous and luetic granulomata and ulcers. An excessively long uvula, very large or infected faucial tonsils, or pharyngeal adenoids may lead to air swallowing. A common cause is chronic catarrhal of the nasopharynx and accessory sinuses. The persistent mucoid discharge running down the posterior wall of the pharynx induces repeated swallowing efforts. The mucous membrane is irritated in pharyngitis sicca. Eye diseases with lachrymation may cause increased swallowing of fluids passing through

the lachrymonasal ducts. Oronasal deformities predispose to air swallowing. Any chronic oral irritation may lead to salivation and when the saliva is swallowed excess air is introduced. Oral irritation may be from diseased gums, teeth or mucous membrane, from tobacco, chewing gum or tooth-picks, or indirectly from the use of mercury and iodides internally. Irritating gases have a tendency to cause air swallowing through the induced rhinorrhoea and choking that occur at times. During hay-fever season susceptible individuals may swallow the profuse oronasal secretions and take in enough air to cause flatulence.

Now the activity of the entire alimentary canal is affected by lesions at any point between the mouth and the anus. Carious teeth may lead to increased intestinal motility. Undigested food thus reaches the large bowel where gas is generated. When such a condition exists, not only is the gas volume increased by excessive air swallowing as described above, but the gases which entered the stomach with the food are hurried through into the colon before they can be disposed of by intestinal absorption. Thus gases swallowed in ordinary quantities may lead to flatulence when local alimentary lesions exist.

This brings us to the second and largest division. Gas may not be swallowed as such in the food, but may be generated within the lumen of the alimentary tract.

#### GAS GENERATED IN THE BOWEL

Some gas is customarily present in the large bowel after a night's undis-



turbed sleep, generated by the action of colonic bacteria on food remnants in the caecum. This may be passed at stool. The longer food remains subject to the action of intestinal bacteria, the more gas there is formed, hence flatulence may be noticeable after going awhile without the customary bowel movement. Much of the colonic gas is absorbed through the healthy bowel wall, into the blood stream, and done away with by means of chemical reaction or excretion through the lungs. A constipated individual may have a disagreeable breath from intestinal gases.

*Gas generated in the lumen of the alimentary tract comes only from food or from necrotic bowel lining.* The commonest cause of flatulence lies in the fermentation or putrefaction of material that has been ingested.

Normally, ordinary articles of diet such as cooked potatoes and tender meat are acted upon by juices in the stomach and small intestines, spend a sufficient amount of time here for proper digestion, and after about two hours the remaining material that has not been absorbed gets into the caecum. Here, in liquid state, further absorption occurs and the cellulose-covered starch granules that escaped in the upper intestine are broken down by colonic bacteria. If for any reason *food is hurried through the small intestine*, much undigested material reaches the caecum. Likewise, if there is *deficiency of alimentary juices* any place along the way, certain food elements reach the caecum undigested and become suitable pabulum for bacteria. Thirdly, if *obstruction* occurs at any place in the intestinal

tract, the food elements in the bowel lumen at the time become subject to bacterial decomposition and with the impoverished circulation which necessarily accompanies such stasis there is deficient secretion of digestive juices and deficient absorption of digested material.

Certain foods resist the digestive action of the gastric and duodenal juices, but are readily broken down by bacteria that normally inhabit the colon, with the liberation of gas. Dried beans and the coarse vegetables are examples. The starch granules of dried beans have thick coverings which are acted upon only slowly by succus entericus. The excess cellulose in lettuce, celery, cabbage, radishes and spinach leads to colonic fermentation. Gases generated from such foods usually have a penetrating but not foul odor, and consist mainly of acetic acid gases and carbondioxide.

Certain materials exert a chemical irritative effect on the bowels. These may be ingested, or may be excreted directly into the bowel lumen through the bowel wall, from the blood stream.

Poisons that reach the bowel lumen by way of the blood stream may have been inhaled in the form of noxious gases, or generated in the body itself. In nephritis poisons are vicariously excreted through the bowel. In diabetes and cancer, chemical irritants may gain access to the bowel from the blood stream, and in many high-grade infections and toxemias such a situation frequently exists.

The commonest manner in which chemical irritants are applied to the alimentary tract, however, causing

rapid peristalsis so that undigested food is hurried into the colon is by oral ingestion of irritating substances. These may be in the form of drugs known as cathartics. Many cathartics, as rheum, have been prepared from articles of diet. Castor oil is expressed from the castor bean which is used for food in parts of the world where it is grown. Some cathartics are made from wild apples, and the ordinary commercial "eating apple" has a more or less pronounced chemical irritant action in the alimentary tract. The internes at Presbyterian Hospital used to call applesauce "Dr Sippy's cathartic."

Foods in particular that cause rapid passage of material through the small intestine are cabbage which is also as before mentioned a resistant article of diet preserves whose irritative action is partly due to complex carbohydrates, maple syrup and honey which contain carbohydrates that are not only active chemical irritants but are also poorly hydrolyzed by succus entericus. Some of these complex carbohydrates reach the colon where bacteria act upon them liberating more gas. Poison meats are so strongly irritating that a distinct inflammatory reaction or enteritis is frequently produced. Decomposed foods in general have a similar action, and the so-called ptomaines are responsible for much of this chemical irritation.

The foods just mentioned also frequently irritate the large bowel. The gas generated in the colon becomes an irritant in itself, and flatus is passed.

Agar and mineral oil, considered harmless inert laxatives, may be pres-

ent in such large quantities in the bowel lumen and so thoroughly coat small food particles as to interfere with digestion. The undigested bits reach the caecum where bacterial action yields gas.

The small intestine may be irritated with resulting increased peristalsis from focal lesions of the stomach, duodenum and ileum. Ulcer of the stomach is frequently accompanied by increased peristalsis, and the symptoms presented may be wholly those of a bowel disturbance, and not in any way specific to gastric ulcer. Duodenal ulcer and pyloric carcinoma may have a similar effect. Catarrhal inflammation of the upper part of the small intestine may lead to excessive peristalsis. Flatulence has occurred with extensive burns, poisoning by mercury, and in purpura. Benign tumors such as melanoma, angioma and the pedunculated lipomata that occur in elderly individuals may lead to flatulence in similar manner. Duodenal diverticuli may cause excessive peristalsis, as may also herniae at the ligament of Treitz, ptosis and kinks. The duodenum may be compressed sufficiently, at the point where the superior mesenteric vessels course over it, to lead to irritation and increased small bowel peristalsis. A not at all infrequent cause of flatulence is some lesion of the gallbladder or ducts such as stones, chronic inflammation or cancer. In a similar manner pancreatic cysts, stones and tumors may cause increased small intestinal peristalsis. Pressure applied to the bowel any place from the cardia to the anus may be sufficient cause for aggravated movements. This pres-

sure may be from growing tumors such as retroperitoneal sarcoma or hypernephroma from benign and malignant neoplasms of the ovary or uterus, from a gravid uterus, from a distended bladder, or from large hydatid liver cysts. Abdominal aneurysm may exert sufficient pressure to bring about increased intestinal peristalsis.

Where increased intestinal motility is associated with abdominal swellings, not only local pressure against the intestine but also local circulatory disturbances that have been induced must be taken into account. When the abdominal circulation is embarrassed in any manner, both secretion and absorption suffer. With faulty secretion of digestive juices, food particles escape to become pabulum for colonic bacteria, and decreased absorption also permits food to reach the caecum. There are many causes of embarrassed circulation, both general and local. A general impoverished circulation may depend upon heart lesions with which high blood pressure is frequently associated. It may depend upon obstruction in the lesser circulation through the lungs from fibrous tissue, fluid in the pleural cavity, collapse of the lung, solidification or cancer. Portal obstruction accompanying cirrhosis of the liver may lead to damming back of venous blood in the mesenteric vessels with consequent poor nutrition of the bowel walls, and diminished or faulty secretion, absorption and motility. Obstruction of the portal vein by pressure from a growing tumor, or thrombosis, or mesenteric arterial embolism or sclerosis are examples of locally impoverished circulation.

Another cause of flatulence, follow-

ing in sequence that just described, is the defective secretion of alimentary juices. Normal secretions from healthy alimentary glands digest food, inhibit bacteria, and apparently neutralize toxins. From the gastric mucosa come pepsin and chemicals that give rise to hydrochloric acid. These digest fibrin, hydrolyze polysaccharides, and inhibit bacterial growth. In the duodenum is succus entericus with protein-splitting and fat—and sugar digesting material from the pancreas and biliary passages. If there is deficiency of hydrochloric acid (achlorhydria) certain bacteria are permitted to enter the intestine noninhibited where their activity may give rise to gas. Certain polysaccharides and fibrin are not digested in achylia. Thus in chronic high-grade anemia, cancer of the stomach and debilitating diseases with which this is characteristically associated, undigested food elements gain access to the large intestine. Here protein materials are broken down with the liberation of foul alkaline gases, fats yield acetic, butyric and similar acids and gases, and carbohydrates acetic acid and carbondioxide. Fats escape biliary digestion when the ducts are obstructed or there is dearth of liver parenchyma. Ordinary proteins such as muscle fibers escape digestion when there is obstruction to the pancreatic ducts as in cysts, cancer of the head, and stones.

The intestinal flora as a rule depends upon the type of food available. Acid-withstanding organisms are in the milk-fed infant's colon. Large numbers of *B. Welchii* infest the colon of those suffering from achylia. With but few exceptions, the colonic bac-

teria themselves are not responsible for excess flatus. Their continued existence is dependent upon the pabulum and the state of health of the intestinal walls.

The walls of the large bowel may undergo changes which lead to the production or passage of excess gas. Here again, there may be *poor absorption* of gases because of the injured lining or chronic congestion. *Too rapid passage* of gases to the exterior may result from increased peristalsis. It is possible, also, that disease of the colonic glands with *defective secretion* may permit excessive generation of gas.

Diseases of the colonic wall itself that lead to flatulence are carcinoma, strictures and ulceration. Ulceration is due to tuberculosis, syphilis, amoeba, and possibly diplobacilli. There are several systemic conditions such as deficiency diseases, nephritis and diabetes in which so-called "nonspecific ulceration" of the large bowel occurs.

Diverticuli and benign tumors may be sources of irritation and gas normally absorbed in the caecum may be passed. In tuberculosis of the peritoneum covering the colon or of the colonic lining, decreased intestinal motility usually occurs. This also happens with syphilitic and carcinomatous ulceration, and stools are retained with generation of excess gas. There are certain cathartics whose action is chiefly on the large intestine. Phenolphthalein is one of these. The resulting flatulence is due to excess motility.

Gas may be poorly absorbed from the large bowel because of impoverished blood supply, especially when

pelvic lesions lead to local congestion. Undoubtedly more than one factor is concerned here, for when pelvic inflammation exists there is irritation of the adjacent bowel wall, reflex nervous disturbances in the colon, and chronic active congestion. Malposition of the uterus may lead to flatulence.

*Paralysis* of the large intestine may cause flatulence. The causes of paralysis are numerous. Some have already been named, local bowel lesions such as appendicitis, tumors and ulcerations. Peritonitis—either suppurative, tuberculous, or carcinomatous—eventually leads to paralysis.

A great many lesions of the central nervous system may be responsible for flatulence. Transverse myelitis, spina bifida, hematoma and the granulomata which produce local pressure against the spinal cord may cause lessened colonic motility. The spinal cord may be compressed by accidental dislocation or fracture of a vertebra, by caries or osteomalacia. Metastatic tumors to the vertebrae notably from the breast and prostate gland may press upon the spinal cord leading indirectly to slowed peristalsis and flatulence. Syringomyelia and multiple sclerosis should be mentioned.

Interference in the reflex segmental arc may lead to lessened movement of the intestine. This occurs in tabes, anterior or posterior poliomyelitis, and peripheral neuritis. Encephalitis and meningitis may lessen large intestinal motility, and cord changes are frequent in diabetes and pernicious anemia.

An irritative nervous influence may be exercised upon the intestine. Men-

tion was made of this when discussing the air-swallowing habit. Emotional states frequently lead to flatulence, undoubtedly through activity of the automatic system. Since the autonomic system is intimately connected with the endocrine system, flatulence can occur during the adjustment periods of life in adolescence, the catamenia, pregnancy and the menopause, with diseases of the thyroid, suprarenal and pituitary glands. Insanity from syphilitic paresis, senility or dementia praecox may be accompanied by flatulence due indirectly to nervous disturbances.

Splanchnic congestion occurs in vagotonia. There is frequently reflex spasticity of the large bowel with sexual excitement.

#### GAS EXCRETED FROM THE BLOOD

One more group of cases of flatulence should be mentioned, that in which there is vicarious excretion of gases through the intestinal wall. After ether anesthesia the flatus passed

may be ethereal. Ordinarily the lungs excrete gases, but when these organs are extensively destroyed or damaged as in pneumonia, cavitation or collapse, gases may be excreted through the colon. When the body is saturated with gas, excretion is partially by way of the bowel but most of the gas passes out through the lungs. Foul gas may be eliminated vicariously when the body is saturated by absorption from some extensive gangrenous region. In gangrene of the lungs there is saturation with gases and damaged pulmonary tissue. If the bowel wall is relatively intact much of the poison gas may be excreted through it. Vicarious elimination possibly also occurs with severe hepatic lesions and in advanced renal disease.

It would seem in this outline that there is repetition, but many of the causes of flatulence overlap. It emphasizes the fact that flatulence and its individual causes is by no means a simple condition.

# Diagnosis and Treatment of the Anemias\*

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OUR knowledge of the diagnosis and treatment of anemia has developed to a large and important extent during the past two decades. The treatment of anemia has been dealt with so completely in recent literature that I shall discuss in this paper chiefly the diagnosis of anemia.

The diagnosis of anemia in a marked case is so apparent that one may be surprised that I should care to discuss the topic at any length. The fact is, however, that in the milder cases of anemia the diagnosis may be beset with difficulties and give rise to clinical pictures which are most perplexing. Even in what might be called mild cases of anemia, the patient may be wrecked with a cord lesion, multiple neuritis, mental deterioration, and other complications which mask completely the symptoms of the anemia itself and which often lead to error in diagnosis. In fact, it is common in cases of this sort for the anemia to be overlooked entirely even by careful internists.

In the early days of medicine, physicians were accustomed to diagnose anemia on the basis of the changed color, that is by observing

pallor of the skin and membranes. With the development of laboratory methods, this simple direct method of examination has been sadly neglected. This is unfortunate because laboratory methods at best are not at the disposal of all physicians and more unfortunate still, they frequently mislead the physician using them to such an extent that he may not discover the actual status of affairs. Red counts, hemoglobin estimations, and examination of the cells of the blood have been used extensively for many years. More recently, Rowntree and his associates have given us a method for estimating blood volume which they believe is accurate and simple enough for clinical purposes and which they believe should add to the accuracy of laboratory methods in gaining an idea concerning the status of the blood. Unfortunately, our old idea that red counts and hemoglobin estimations tell the whole story concerning the status of the blood is not correct. A person with a normal red count and hemoglobin per cent may be either anemic or plethoric due to an increased or reduced blood volume.

Rowntree and Brown's studies, while interesting from a standpoint of actual blood volume, do not give us an absolutely dependable means of

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tion was made of this when discussing the air-swallowing habit. Emotional states frequently lead to flatulence, undoubtedly through activity of the automatic system. Since the autonomic system is intimately connected with the endocrine system, flatulence can occur during the adjustment periods of life in adolescence, the catamenia, pregnancy and the menopause, with diseases of the thyroid, suprarenal and pituitary glands. Insanity from syphilitic paresis, senility or dementia praecox may be accompanied by flatulence due indirectly to nervous disturbances.

Splanchnic congestion occurs in vagotonia. There is frequently reflex spasticity of the large bowel with sexual excitement.

#### GAS EXCRETED FROM THE BLOOD

One more group of cases of flatulence should be mentioned, that in which there is vicarious excretion of gases through the intestinal wall. After ether anesthesia the flatus passed

may be ethereal. Ordinarily they excrete gases, but when these are extensively destroyed or absorbed as in pneumonia, cavitation or collapse, gases may be excreted from the colon. When the body is saturated with gas, excretion is effected by way of the bowel but most gas passes out through the lungs. Foul gas may be eliminated vicariously when the body is saturated by absorption from some extensive necrotic region. In gangrene of the lungs there is saturation with gas and damaged pulmonary tissue allows the gas to pass out. In the case of the bowel wall is relatively impermeable and much of the poison gas may be excreted through it. Vicarious excretion possibly also occurs with hepatic lesions and in advanced disease.

It would seem in this outline that there is repetition, but many of the causes of flatulence overlap. It emphasizes the fact that flatulence is not a simple condition.





determining whether or not the volume of blood found in a given case is optimum for the patient under observation or too large or too small. This, theoretically, cannot be determined with accuracy by measurements of height and weight, for as is apparent, an athlete of a given height and weight needs a greater blood volume under normal conditions than a flat phlegmatic individual, such as a case of hypopituitary obesity. This apparent fact hardly needs discussion. Muscle tissues not only contain more blood than fat, but a muscular individual has larger internal organs than a fat individual. The heart, large vessels, the liver, and the spleen, etc., which contain enormous quantities of blood should give rise to a disproportion in blood volume between muscular and fat individuals which could hardly be estimated theoretically by measuring height and weight.

We are confronted with still greater difficulties when we try to determine whether a given blood volume is optimum for a patient who has a pathologically increased cardio-vascular space which must be filled and which therefore, demands a greater blood volume for the optimum per unit of weight than would exist in patients who might not have such an anomaly. For example, a patient with a largely dilated heart or an aneurism, or enormous varicose veins, should have, to be optimum, a larger blood volume than a patient who has a normal sized heart and vessels. Furthermore, in patients whose weight is pathologically increased as we observe in patients with osteoplastic tumors, the blood volume to be optimum should

be smaller per unit of weight than it is in patients who do not have osteoplastic tumors.

In pernicious anemia, we have an anomaly which leads us still further astray. A number of years ago, Dr. D. D. Stofer and I (1) found that in this disease makrocytes tend to lodge in the capillaries and give rise to a large disproportion between the capillary blood count and the venous blood count. In fact, in an untreated case of pernicious anemia, the capillary count is usually 25% to 50% or more higher than the venous count. This disproportion, we found to be constant regardless of whether the patient had been transfused and had a reasonably high count, or if untreated and had a very low count. Since the introduction of the Minot-Murphy Diet, we find that the two counts in treated cases tend to come closer together, and as the count nears four million, they may be approximately the same.

We must frankly admit, therefore, that in our study of anemia, we are up against variables which are discouragingly gross. This led me many years ago to try to devise a method for studying color which might overcome some of these difficulties. I have described this method in detail in previous papers (2) and need only mention it briefly in this connection.

As previously mentioned, it has been a time honored custom for physicians to decide whether or not a patient is anemic or plethoric by observing his color. Methods of examination for this purpose have not been satisfactory because of the fact that some individuals who are normal have red

faces, and some pale faces. Each may be normal so far as the status of the blood is concerned. The face as an organ of expression varies in color on this account. This is true also of the lips and nails. Furthermore, the skin varies enormously in color because of its important function in the regulating of loss of body heat. When it is urgent that the loss of heat be increased, the skin vessels are likely to dilate, whereas, when it is urgent to retain heat, the reverse status obtains and gives rise to a pale skin. The conjunctiva is not a good place for the observation of color for this change in color with posture. If a person is sitting, a column of blood under negative pressure tends to make the conjunctiva pale. Whereas, if the person is lying down, especially if the head is lower than the heart, the same capillaries tend to be abnormally full because of the effect of gravity. This change in color is quite marked. One can convince himself of this fact if he will compare the color of his two hands, one which has been held above the heart for a few moments and the other below.

There is one skin area in which color varies remarkably little under the usual conditions under which the physician sees a patient, in house, office, or hospital practice. This surface is the palm of the hand. The palm of the hand is different from other skin surfaces in that the epidermis is thick and makes it of little use in the regulation of body temperature. For this reason, vaso-dilation and constriction under the influence of heat and exercise is less useful

physiological and does not occur to the same extent as it does in other skin areas. The fact is, that under normal conditions in normal individuals, the color of the palm of the hand varies remarkably little at different times of day and from day to day. I have compared my own palm with that of several normal assistants a great number of times and find them always almost exactly the same.

To estimate color in a patient, the physician must first be sure that his own color is normal. One can gain an idea concerning this point by comparing his own palm with those of a number of young healthy individuals. If the physician's palm is found to be normal in color, it can be used for comparison with patients. To make the tests, both physician and patient must sit or stand comfortably, each having his hand at about the level of the apex of his own heart or possibly an inch lower. The hands should be semi-flexed and allowed to remain in this position for a few moments until constant color is established. The comparison may then be made. A slight grade of anemia or plethora is so apparent on comparison that it could not escape the notice of even a most casual observer. The removal of as little as two or three hundred cc of blood by venous section or the addition of two or three hundred cc of blood by transfusion gives rise to a change in color which could not escape the notice of a casual observer.

I can assure the reader that this method is dependable if made carefully and if the physician has had a little experience. It is well worth

while for any physician to get acquainted with the method and use it with confidence. In my hands, it is equally as valuable as the determination of a red count or percent of hemoglobin if not more so, and is at the disposal of every physician whose own color is normal. It requires no apparatus and only a moment's time. This method has been described in more detail in a previous paper (2).

Given the fact that because of abnormal pallor of the palm, we make a diagnosis of anemia, we should next concern ourselves about the type of anemia which afflicts the patient, for upon the type depends our choice of methods of treatment. This can be determined in a majority of cases through estimation of the blood counts and by examination of a stained blood smear. In the secondary anemias, we have a relatively greater reduction in the hemoglobin percent than in the red count associated usually with a polymorphonuclear leucocytes. In aplastic anemia, we have a reduction in all the formed elements of the blood, red cells, white cells, and platelets. The same status of affairs may be observed in pernicious anemia except for the fact that the reduction in white cells and platelets is not inclined to be so great and the red cells show a distortion in shape and size which is very characteristic of the disease. Most important in this illness is the increase in diameter, thickness and opacity of the red cells. This (so-called makrocytosis) can be observed in the early stages of the disease and is so characteristic as to make it possible to diagnose the disease from a blood smear long before

the red count is materially reduced. In fact, I have observed it frequently as long as six to eight years before the patient became definitely anemic, in fact once when the patient was polycythemic to the extent of a red count of six million five hundred thousand. The finding coupled with an achylia, a history of tingling in both hands and sore mouth should enable one to predict anemia positively one or several years before it appears.

The leukemias can be diagnosed by the finding of a distortion of the differential white count or in the appearance of pathologic white cells. These facts are so familiar to internists that I need only mention them in passing.

There is one type of anemia which I should like to more than mention. This type is pernicious anemia. I could say nothing in this paper which would interest internists in the diagnosis of pernicious anemia after the anemic stage of the disease has been reached. It seems a crime, however, to allow the diagnosis of pernicious anemia to be delayed to any such advanced stage as this. Discovering a case of pernicious anemia after the patient has become anemic is exactly analogous to discover a case of tuberculosis after it has progressed to such an extreme advanced stage that the patient has huge cavities, high fever, emaciation, and is about ready to pass out. Tuberculosis should be diagnosed in its early stages if one wishes to obtain a maximum result so far as the prolongation of a useful degree of health is concerned. Exactly the same statement can be applied to the diagnosis of pernicious

anemia It should be diagnosed eight or ten years prior to the time at which the patient becomes anemic, and at such a time it is relatively easy to make the diagnosis practically with positiveness I wish to emphasize the fact that the diagnosis can be made at this early stage with such accuracy that the patient can be told almost positively he has a potential anemic case and that he must constantly concern himself over matters which may precipitate the condition, matters such as restrictions in diet, infections, mental or physical strain, and excessive exposure of the skin to sunlight

In almost every patient who has pernicious anemia in the anemic stage, one can get a long history of symptoms which are characteristic of the disease which date back five, ten or even twenty years and make one realize that the average case of pernicious anemia should be diagnosed positively at the time of onset of these symptoms and not at the time of onset of the anemia In the average case which is diagnosed on the basis of blood findings, we find a history of symptoms such as tingling of the finger tips of both hands, sore mouth, dyspepsia, characteristic of achylia, and diarrhoea characteristic of achylia In patients who come to a physician complaining of dyspepsia, diarrhoea, peculiar feelings of nervousness or weakness, or sore mouth, one should always inquire concerning numbness and tingling in the finger tips and toes There are very few common illnesses except pernicious anemia which give rise to numbness or tingling in the finger tips in both hands and

especially in finger tips and toes on both sides This phenomenon is most characteristic of impending pernicious anemia especially if it is inclined to be persistent over several weeks or months Furthermore, aphthous stomatitis and a beefy red appearance of the tongue is most characteristic of this disease In fact, a red tongue especially if furrowed and dry and especially if associated with atrophy of the papillae is as characteristic of impending pernicious anemia as a markedly reduced sugar tolerance is characteristic of diabetes Dyspepsia associated with a total lack of hydrochloric acid in the stomach juice is found in almost every case of pernicious anemia after they have become anemic It has been found in almost every case of pre-anemic pernicious anemia (diagnosis proven by later developments) which I have observed A few have shown marked subacidity with a later development of achylia Makrocytosis previously referred to occurs in the earliest stages of the disease There is, furthermore, an increased opacity and blueness which characterizes the appearance of the red cells which can be observed with great definiteness and which to me indicates that the average red cell is closer than usual to the normoblast The increased opacity and blueness which characterizes the makrocyte as compared with a normal red cell characterizes also the blasts as compared with normal red cells

The above syndrome of symptoms can often be observed in the family of patients who have advanced symptoms of pernicious anemia The symptoms, furthermore, tend to vanish on

a Minot-Murphy Diet For early cases, this usually takes a period of about two months or more The only cases of aphthous stomatitis which I have actually benefited by therapy have been cases of this sort which I have found to be associated with achylia and other symptoms which I thought indicated that that patient was a potential case of pernicious anemia In these, the stomatitis has been relieved by liver.

Symptoms which occur at a later period but which also antedate the onset of the anemia for one or several years, are atrophy of the papillae of the tongue, disappearance of the normal roughness of the skin of the forehead, a tendency to a ruby-like transparency of the lips (caused no doubt by atrophy of the epithelium of the lips), and a tendency to vague pains between the joints which cannot be accounted for by arthritis, subdeltoid bursitis, or other anomalies of the sort It is by no means uncommon for a patient in the pre-anemic stages of pernicious anemia antedating one or many years the onset of the anemia to complain of vague pains which may baffle the physician completely The pain may be mild or in many cases may be very intense—in fact, in one patient observed by the writer pains in the extremities had been so intense as to confine the patient to bed for months at a time The case had been diagnosed multiple neuritis by almost every physician who had seen her In fact, this diagnosis was correct except in the fact that the primary source of the multiple neuritis had not been discovered until the patient was a total wreck—

far beyond the desirability of prolongation of life. Even at this stage, the blood count was not materially reduced nor was the patient pale. Makrocytosis, achylia, stomatitis and atrophy, however, made a positive diagnosis as simple as abc

As previously mentioned, in pernicious anemia there is a tendency for the large makrocytes to lodge in the capillaries This phenomenon gives rise to an abnormally red appearance of the patient and may for years obscure the real disease from which the patient suffers This is abnormally marked if the superficial epithelium is atrophied to such an extent that the skin becomes translucent and allows the accumulated red cells to show their color more clearly The average patient with pernicious anemia prior to the appearance of anemia or even after the red count has been reduced to three and one-half or four million or less has an abnormally red or ruby color This may be unusually marked if the count is not reduced, or especially if it is increased, as it occasionally is, to five and one-half million or six or even six and one-half million In cases of this sort, one can convince himself of the existence of an impending anemia by comparing capillary blood with venous blood The diagnosis of the condition in this stage is most important because of the fact that it is in this stage that most can be accomplished so far as the prolongation of a useful state of health is concerned There is generally and unfortunately a mental deterioration which accompanies pernicious anemia and which may appear at an early stage It gives the

patient a child-like personality and manner of speech which to me indicates deterioration of cortical cells and which if once thoroughly and well established is likely to persist. If we are to prevent the development of mental changes and cord changes which cannot be cured by transfusion, liver therapy, or what not, we must discover the disease before an advanced stage is reached, that is before these changes have manifested themselves as an evidence of actual cell deterioration.

The fact is that the disease can be discovered easily and with definiteness in the pre-anemic stage and I firmly believe that it is as urgent for the physician to discover cases in their incipency and to get them under a useful method of therapy, as it is to discover tuberculosis in its incipency and to get the patient under proper treatment before irreparable damage has been done.

This paper has been largely devoted to the diagnosis of anemia for as previously mentioned the treatment of anemia has been dealt with at length in recent literature. I feel that liver therapy has a most important place in the treatment of anemia especially in the pre-anemic stages. I feel sure also that it has a permanent place in the treatment of pernicious anemia after the anemic stage has been reached. I do not feel convinced, however, that transfusion should not also be used and pushed to the point of restoring a reasonably normal color in the paler patients. It hastens recovery and does no harm, if the size of the transfusion is kept below a point which causes capillary hemor-

rhage. Massive transfusions in pernicious anemia are dangerous. Transfusion of one or one and one-half pints at three or four day intervals repeated to the point of nearly restoring, but not completely restoring normal color in the palm of the hand is a safer procedure especially in the more severely ill patients. No effort should be made to restore the red count by this means, for so long as a patient has makrocytosis he is better off with a red count of three or three and one-half million than he is with a count of five million. This statement is based upon a very broad clinical experience in which transfusions were used consistently for many years before the advent of liver therapy. In the presence of marked makrocytosis a count of five million to me indicates plethora and an unhealthy situation. I have known of advanced cases with extreme makrocytosis in which color was normal and the patient better off when the count was as low as two million five hundred thousand.

Whereas, some physicians have questioned the usefulness of transfusion in the treatment of pernicious anemia, none could with reason question the usefulness for transfusion in the secondary anemias and aplastic anemia and in severe anemia caused by leukemia. In the secondary anemia, transfusion is an immediate and permanent cure if the cause of the anemia can be found and removed. It is a complete cure if pushed to the point of restoring normal palm color. It is absolutely safe if the donors are properly typed and can be pushed to large volumes without harm. This

represents one of the most sensation-ally specific, quick and complete cures with which we are acquainted in the practice of medicine. Out of a great number of cases which I have transfused, I do not know of one solitary case which has been harmed by it and nor do I know of one solitary case which was not permanently or temporarily benefited by the procedure.

The indications for transfusion are two-fold if the patient has a debilitating disease such as typhoid, tuberculosis, chronic bleeding ulcer, or a debilitating disease. Here it is urgent that the tissues be supplied with a quantity of normal corpuscles adequate for the purposes of supporting a normal functional capacity of the organs and for the healing of tissues.

#### CONCLUSIONS

Anemia can be diagnosed simply and accurately by examination of the color of the palm of the hand according to a technique which is described.

Pernicious anemia can be diagnosed with definiteness many years before

the anemic stage is reached—in fact pernicious anemia is a very chronic disease, the anemic stage of which could almost be called a terminal event. Treatment in the pre-anemic stage is most satisfactory and prevents the development of brain and cord lesions and other complications which when once established do not yield well to therapy of any sort.

Transfusion hastens recovery of advanced cases, but must be used with care in pernicious cases. My results agree with those of other observers concerning the usefulness of liver therapy.

Transfusion is an immediate, complete, and safe cure for secondary cases and chlorosis and is permanent if the primary cause of the anemia can be found and removed. It is the prince of all specifics if strongly indicated and if technique is flawless. It is especially indicated in debilitated cases and in patients who have other diseases which demand an adequate supply of blood to the tissues for prompt function and prompt healing.

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# Liver Diet in Pernicious Anemia\*

By HILDING BERGLUND, M D, *Minneapolis, Minnesota*

I WILL confine myself to a few points I wish to bring out. Yesterday you had the opportunity to listen to the splendid presentation of Dr Sturgis, relating in a clear way the surprising and satisfactory results that one, as an unbroken rule, meets when treating pernicious anemia with raw calf liver, or with the liver extract that is now available, thanks to the work of Dr Kahn operating with Minot and Murphy. I will only add that there seems to be some differences in the results obtained. We had better be careful in our statements because we have such short experience so far that those of today may be amplified by further experience. There is some difference between the treatment with raw liver and that with liver extract, this is not surprising when we consider that the liver in the body is an organ which contains the greatest number of powerful enzymes. The difference seems to me that when we feed raw liver when the patient is about halfway back to normal, there seems to be, without any exception, the development of marked eosinophilia, which may reach 4,000 cells per

cm. This we have not met in any case treated with liver extract.

We also have to remember that the liver extract we are using today is not at all a definite product. The purification is going on in Dr Kahn's laboratory, and instead of the yellow powder, Dr Kahn has now produced a white amorphous powder with less than one-half gram per cc, with correspondingly less active power.

What do the wonderful results we obtain mean when we try to correlate them with our results in pernicious anemia? It is important to remember that what we call pernicious anemia is a disease characterized by much more than the anemia. The three important features are the achylia, the subacute combined degeneration of the spinal cord with changes in the central and peripheral nervous systems, and the anemia. The question immediately presents itself, which of these symptoms is influenced by the liver diet? Then it seems clear that only the anemic condition is influenced. The achylia remains unchanged after the patient's blood has entirely recovered. Many of you have already seen that in the cases that show the beautiful improvement of the blood the spinal cord symptoms may continue to progress, sometimes rapidly. Also, that we get a

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response in the blood in cases in which there is not only very little change in the blood picture, but also with the most outspoken nervous symptoms. The patients are invalids, and yet the blood picks up in an entirely independent way. This is not without importance in our attempts to define the nature of the whole picture of pernicious anemia.

How long will this improvement last? Evidently no one knows, since the liver diet has been used only three or four years and the extract less than a year, but so far we know of no reason why it should not be continuous with the continued administration of liver extract even after the blood has returned to normal. It should be possible by the continued administration of extract to keep the blood permanently in a satisfactory or normal condition. The experience of the next few years will prove whether this position is correct or wrong.

What other anemias are influenced by the liver extract? As far as we can to date express an opinion the only anemia that is influenced is the anemia that we know in the last few years as more or less identical with the blood picture in pernicious anemia.

As to the secondary anemias, what of those? There we have to consider that what we call secondary anemia is far from a uniform group. They undoubtedly contain many different things, but so far as the blood formation and the blood picture goes they should fall into one group. I have had, and others have had a not too limited experience with the secondary anemias that one sees in middle aged

or a little less than middle aged women. I have studied such patients and in my experience the patients have been more or less cooperative. I have tried the raw liver and we are now trying the liver extract, but in spite of adherence to the liver diet for weeks or months it has left the anemia untouched. There are a few cases that might be thought to respond, but there are cases that by competent hematologists one year are diagnosed as secondary anemia, and the next year as pernicious anemia. These cases are rare but they have been observed by hematologists in different parts of the world.

Where does this lead us in regard to a theory for the action of the liver extract? Minot and Murphy have suggested that the chief action is the bringing about of the final stage of maturity of the red cells. This is attractive if we consider that the bone marrow is filled with bright red cells crowded with hemoglobin, but also containing a nucleus which the bone marrow is able to finish and get rid of the nucleus and discharge into the circulation. If we consider that what is being done by the liver is the maturing of the cells, that is an attack on the finishing of the red cells, we should think that the extract contains a normal body constituent that perhaps has nothing to do with pernicious anemia. If that is true we should expect to obtain similar results with normal individuals. In our laboratory three of our staff, two ladies and one young doctor, all healthy individuals, have been taking three vials a day of the liver extract

We have not had so much response of the reticulocytes as in pernicious anemia, but there has been a rapid increase in the red cells, from 4,200,000 and 4,500,000 before the diet, up to 6,200,000 and 6,600,000 on the tenth day. Then, in all of them it dropped to the neighborhood of 5,000,000 on the seventh day, and then up to 7,000,000. We are continuing these experiments on normal individuals, but it has been difficult to obtain the liver extract in sufficient amounts.

This little observation is, I think, of great significance because it confirms our previous assumption that the liver extract is something that normally plays a rôle in the final maturing of the red cells.

Can we go any further in our theory? I think we can, even if it takes us into still deeper water. When the body develops there is, of course, a morphological development and a chemical development. Ordinarily when we study our body we see the morphological and the chemical developments going parallel in a normal way. During the blood formation in the fetus when the primitive blood formation takes place the chemical development is ahead of the morphological development, so that the cells are crowded with hemoglobin in their development, when the nucleus is very immature. Therefore, in the embryonic life the chemical development of the blood is ahead of the morphological, but later on we get the normal blood picture. In pernicious anemia, as Ehrlich brought out

in the '80's, we revert to the former condition, so that the hemoglobin then seems to be undisturbed. Every cell contains enormous amounts of hemoglobin that make the cell larger. In pernicious anemia we seem to be able to interpret that as a return to the morphological element of the cell rather than the chemical element. In the secondary anemias we have the contrary. There is no disturbance of the primary character in the morphological red cells, but a definite weakness in the manufacture of hemoglobin. That is why we call it a secondary anemia with low index.

If this outline is correct, then we should not expect to get any effect of the liver extract on the chemical manufacturing process. It therefore should leave the secondary anemia untouched, since it evidently affects the morphological phase of the blood formation in pernicious anemia. It is the morphological phase in which we have our trouble.

You will make the criticism of this suggestion that it is made after we have made our observations. Evidently it is, as with most theories. It is also clear that it is vague and the only excuse for taking your time to listen to it is that it may serve to stimulate thought. The fact that we have come up against such interesting facts as we have in the liver diet should not be held against the speaker. It proves in the best way the magnitude of the discovery of Minot, Murphy and Kahn.

# The Scientific Spirit\*

By PROFESSOR MARTEN TEN HOOR, *Tulane University, New Orleans, Louisiana*

WHEN a layman enters the professional presence of a physician, he does so in humility, and possibly even in fear and trembling. Since even a philosopher or a student of philosophy cannot endure the toothache or any other ache patiently, he must also occasionally enter this imposing presence and he too cannot but experience this feeling of timidity, a timidity not unlike that of the penitent approaching the confessional, since it has for its cause fear of the coming diagnosis and of the subsequent prescription of treatment. When a student of philosophy has the temerity to address a whole "College" of physicians, his fears are not only quantitatively multiplied but they are also qualitatively altered, because to his natural layman's respect for the professional expertise of his audience there is added, as a complication, considerable doubt as to the attitude of his audience to philosophy.

Philosophy has a rather mixed reputation with the layman. Those who have never studied the subject either have a tremendous respect for it or they have no respect for it at all. Those who have studied it systemati-

cally and intelligently have their respect tempered with a certain amount of decent disrespect. Some of these serious students of philosophy are even inclined to agree with Omar when he says,

"Myself when young did eagerly frequent

Doctor and Saint, and heard great argument

About it and about, but evermore  
Came out by the same door where in  
I went"

There are even apostates who have come to accept Michelet's dictum that "metaphysics is the art of systematically deceiving oneself."

However, the timidity which I as a layman and as a student of philosophy feel in your collective professional presence is as nothing compared with the fear and trembling which, as a boy, I used to experience in the presence of a quite different kind of internist. In my boyhood our family was visited, once a year, by the minister, on the occasion of what was known as "house-visitation." At this time all the members of the family were subjected to a searching spiritual examination, to be followed by diagnoses of the state of our respective souls. Finally, treatment...

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prescribed where necessary I assure you that our childish fear of the mysterious knowledge and desperate technique of our family "physician of the body" was as nothing compared with our fear of the powers of this family "physician of the soul"

Now in our day no one would ever think of confusing these two types of "physicians," so sharply have their respective techniques and their professional activities become differentiated. In fact, sometimes their contemporary relations are not entirely amicable. And yet they were at one time one and the same individual. I propose to introduce my topic with a brief and somewhat playful survey of the history of the changing relations of these two types of "internists"

In the person of the primitive "medicine man" we find the ancestor of both types. This versatile dignitary attended to the needs of both body and soul, his technique being a combination of magic, incantation, and native shrewdness. But soon there occurred a phenomenon analogous to cell-division and differentiation of function so characteristic in the development of organisms. The medicine man "divided" into two: the ancestor of the physician of the body as we know him, and the ancestor of the physician of the soul. The latter soon developed into a philosopher-theologian who seems to have been the spiritual progenitor of the house-visitor of my boyhood. Each of these two new professions claimed diagnostic and therapeutic powers.

This division of interest and of labor was sharply emphasized by

mediaeval theology, with a consequent evaluation and ranking of the professions quite different from that generally accepted in our day. The body was adjudged of the earth earthy and, since it had only a short while to live, of temporary importance only. Affliction and disease were accepted with equanimity, by some enthusiasts even with rejoicing, since it was believed that God thus punished those whom he loved. Philosophy, which was in this period the humble handmaiden of religion, sought, and thought it had found, theoretical justification for this discriminative attitude to the body and to the profession attending its ills and ailments.

The physician of the body was naturally at a tremendous disadvantage. What, after all, was a temporary bodily pain—or even a lifetime of bodily suffering—compared with eternal damnation? When considered professionally, the physician of the soul had a great advantage. In diagnosis, all symptoms indicated one and the same ailment: original sin. The physician of the body, on the other hand, was faced daily with a baffling number of diseases, in fact, new ones were constantly appearing.

In the matter of treatment, too, the physician of the soul had a great professional advantage. The treatment for original sin was the prescribed way to salvation. There was ready an accepted body of revealed doctrine to guide the profession. No new treatments were permitted. Originality in this meant excommunication at least. Every bishop was a kind of sanctified Dr. Fishbein. The physician of the body, on the other hand,

had no choice but to work out his problem empirically. There was no official *materia medica*, not even much of an unofficial one.

In professional standing the physician of the soul stood supreme, since he had a divine commission, received and insured through the mediation of the church hierarchy. The physician of the body sometimes did not even have a diploma. In the matter of results, it was again the physician of the soul who had the advantage. Strictly speaking, he never lost a patient since the soul was immortal. Consequently he took no risk in prescribing and he never had to attend post-mortems. Nor could the patient's permanent condition after treatment be ascertained since sooner or later he left for another world. The physician of the body, on the other hand, lost an occasional patient, to put it mildly. His failures were recorded in marble and stone. Even his successes were insecure, since relapses were possible.

The result of all this was that there was little official encouragement, by religion and philosophy, of scientific observation and experiment in medicine. Philosophy had little interest in science. But then came the next stage. Philosophy declared its independence of theology because it resented the constraints put upon it and insisted on trying its own wings. One of its first attempts at independent investigation was directed at the analysis of the soul. Thus psychology developed.

But then a very interesting thing happened. The soul, which was the patient being diagnosed, did not exact-

ly expire during diagnosis, but what was much more embarrassing, it evaporated. Psychology tried to be scientific and independent and promptly lost its bearings. Ever since this embarrassing disappearance of the patient, psychology has had a rather exciting and disturbed career. Having found the soul too volatile or too ethereal for scientific study, it announced that it was engaged in an analysis of mind. But this concept, too, it found embarrassing and difficult of definition, and so substituted for the concept of mind the concept of consciousness. In our day even this has been discarded, the psychologists—at least some of them—insisting that psychology is nothing more than the science of behavior. A wit has epitomized this history of psychology thus: "Psychology first lost its soul, then it lost its mind, then it lost consciousness and now it has only behavior left."

Fortunately, this experience with the attempt at a purely theoretical analysis of the soul taught philosophy a lesson: the need of a new intellectual spirit and of a new method. While philosophy had been learning this lesson, science had been quietly and steadily developing as an object lesson in the new spirit and the new method, thus adding a moral to the tale. Whereupon there arose among philosophers an enthusiastic—in fact, possibly a bit over-confident—exponent and champion of the scientific spirit and the scientific method, Francis Bacon. Since Bacon's day, philosophy has never entirely resigned this rôle and in our own day there is probably no problem in which philoso-

phers take such enthusiastic interest as the problem of science

This history is to us moderns only mildly interesting, so accustomed have we become to the acceptance of science and its methods. The old quarrel between science and religion seems out of date, even when it is revived and when it becomes for months the featured news in our public press. Yet we must not forget that the quarrel had its tragic side. Many obstacles were placed in the way of free scientific development. Scientists were ruthlessly suppressed and even persecuted for their loyalty to their ideals. But the victory of the scientific spirit cannot be denied. Such a meeting as this is eloquent testimony to this victory, and hence it seemed to me a fitting occasion for attempting a brief analysis of this spirit.

What is the scientific spirit? Let us examine it by contrasting it with the spirit which so long opposed it, which we may call, for purposes of identification, the dogmatic spirit. From one point of view, both seem to be mental tendencies or attitudes, from another point of view, they seem to be mental habits. The dogmatic spirit begins with certain principles which are accepted as true on some other ground than observed or experimentally demonstrable and verifiable facts. Hence we call such principles, "dogmas." The facts are subsequently interpreted in the light of and in terms of these dogmas. The following illustrations exhibit the dogmatic spirit. (1) The scientific theory that some diseases are the result of the more or less accidental introduction of

micro-organisms into the body was at one time emphatically opposed by certain theologians, on the ground that disease was a special punishment sent by God and that therefore it could not be the result of accidental infection. Granting for purposes of economy in this discussion that the dogma and the theory are contradictory, we cannot fail to note the surprising indifference to scientific observation and experiment here exemplified. (2) As late as the early 18th century the following argument was advanced in defense of the Principle of the Conservation of Energy, a principle which was later experimentally demonstrated. "There are two ultimate principles or elements of Being, Matter and Energy. Now we already know that Matter is conserved. If God created Matter so that it could not be destroyed, how much more certain must it be that Energy, which is the spiritual principle, cannot be destroyed."

(3) The third illustration is contemporary and is advanced, incidentally, to exhibit the extravagances being perpetrated by enthusiasts in the field of psycho-analysis, as well as primarily to give an example of the dogmatic spirit at work. If you should go to one of these enthusiasts and report that you had had a dream 'featuring a bearded cow eating pink apples under a huge tree on a beautifully rounded hill, it would certainly be interpreted to mean well, let the reader give his own interpretation, being sure that the heart of it is a sex-complex, the more scandalous the better. It seems to me that we have here a good illustration of the habit of beginning with a dogma and interpreting facts in terms of it.

The scientific spirit or habit of mind, on the other hand, begins with brute facts, whenever possible, then proceeds to tentative principles, which are called hypotheses, and then returns again to facts. Now at this point I might well be interrupted with the question, "But what is a fact?" In a meeting of philosophers I would scarcely have dared to use such a simple term. If I did inadvertently do so, it would mean, as far as the real subject of the discussion is concerned, a profitless evening and a sleepless night. However, I have no professional scruples here and I don't mind indicating in a very simple way what I mean. If you drink some carbolic acid and subsequently suffer agonizing pains, I take the acid before you to be a fact, also the drinking of it, also the pain and the connection between the two. If you see evidences of much philosophical looseness here and are still in doubt, you have the first symptoms of the disease known as philosophy.

The scientific spirit or habit of mind we may profitably analyze a little further. The following characteristics can be analyzed out. First of all, the scientific spirit is *interested in facts*. Strange as it may seem to the neutral observer, there are minds which are not interested in facts, they are interested rather in protecting their own dogmas. To facts, when they seem dangerous, they take the defensive attitude, which makes their minds impervious to just those facts which they ought most to notice. There are even people whose immunity to facts is so complete as to be almost pathological, facts do not count in their thought and

in their conversation, and sometimes not even in their practices.

Secondly, the scientific spirit is *interested in all facts*. Some people seem to have a blind side to facts, an affliction which is very handy and which often contributes much to the "spiritual" satisfaction and comfort of such individuals. The fact that minds do have such blind sides may help to account for the fact that statistics are so much more useful to the intemperate reformer than to the scientist.

In the third place, the scientific spirit *observes facts*. It trusts the senses because it is convinced that they are our only refuge where facts are concerned. However, it knows the limitations of sense-perception and is aware of the errors and fallacies which threaten the mind, but it seeks constantly to reduce this margin of error. It consciously and willingly gives up absolutism and is able to live at peace with relativism. It is not even afraid to confess a certain sane and courageous skepticism, confessing with Goethe that "man is not born to solve the mystery of existence, but he must nevertheless attempt it, in order that he may keep within the limits of the knowable."

The scientific spirit, in the fourth place, is interested in the *analysis* of facts, that is, it is interested in reducing facts, wherever possible, to simpler and more fundamental facts. The discovery of the disease we now call typhoid fever was no doubt important, but more important was the discovery of the bacilli which we now know to be the cause of the disease. Man's understanding and control over nature increases with analysis, and this manifes-

tation of the scientific spirit brings us close to the heart of science

Fifthly, the scientific spirit seeks to *relate facts to one another*, the particular type of relationship which science is most interested in establishing being that of cause and effect. Charles Darwin insisted that a good scientist must be a good theorizer as well as a good observer. He not only here emphasizes the need of relating facts to one another but he also implies that the first attempt at establishing such relationships is always an hypothesis. It is to the point here to recall that such hypotheses and theories are not dogmas, the difference between dogmas and scientific theories being that the former are at once accepted as true and are not derived progressively from facts whereas the latter are so derived and are not at once accepted as true.

Hence the sixth characteristic of the scientific spirit: the scientist insists on *checking his theories against the facts*. Obviously, this task is never finished, since all facts are never at hand. New facts are constantly being discovered and thus the adjustment and readjustment of theories is made necessary. Finally, the scientific spirit is willing to *submit to facts*. This lesson science has learned only after long, and sometimes bitter, experience. It is hardly necessary to point out that in many fields of human inquiry and human endeavor this lesson has not yet been well learned.

When presented in this rather sophomoric way, the scientific spirit seems very reasonable and the dogmatic spirit very unreasonable. But we must not forget that *we* have several centuries of the development of science and the

scientific spirit behind us. Nor must we forget, in this connection, that the dogmatic spirit is an insidious habit of mind which, in spite of its unreasonableness, has greatly influenced human thinking. The virus of dogmatism was in some way introduced into philosophy, literature, religion, and even science, and the disease, if we may for the moment call it so, held full sway until the scientific spirit was developed as an antidote. It is with the scientific spirit that the dogmatic spirit must be combated, wherever and whenever men are interested in the discovery of truth. We may be sure that there will always be occasion for combat, since the dogmatic spirit is the expression of the tendency, or possibly ~~is~~ the tendency, to defend our religious, moral, social, artistic, and political prejudices.

But the scientific spirit also has its dangers. There is the tendency to forget that inference from facts is always tentative. Science has often brought trouble on itself by assuming an attitude very much like that of the dogmatic spirit. The scientist must never forget that science is cumulative and progressive, and that scientific knowledge is relative and not absolute. Therefore science must always be in a receptive and welcoming mood towards new facts or new analyses of old facts. Science is largely a history of readjustments, corrections, and re-statements, and there is no sound logical reason for assuming that this time is past or will ever be past. The history of medicine is as eloquent an illustration of this as it is possible to find.

The scientist must be quite as willing to give up old theories for better ones, old practices for new ones, the criterion



always being observation and experiment "Back to Facts" must be the watchword of all science, possibly nowhere more than in the science of medicine. Science must be kept plastic in the presence of the existing subject-matter, someone has said. Nowhere is blind orthodoxy more out of place or more dangerous than in the theory and practice of medicine. It must be remembered that heterodoxy is not always wrong. Many men now recognized as great scientists have been outstanding, almost "professional", heretics. Heresy hunting with all its irrationality and extravagances, with its native dangers and its unfortunate by-products, is always a temptation to any organized profession. The good fortune of medical science is that the persistence, the vitality, and the nearness of the facts will always act—and that rather promptly—as a check. But this assumes the interest in and the receptivity to facts named above as characteristics of the scientific spirit.

However, far be it from me on such an occasion as this to dwell at length on the dangers which beset the scientific spirit, either in medicine or elsewhere. It was my purpose rather to celebrate the success of this spirit and to express admiration for this spirit especially as it is exemplified in the science of medicine. Of course, as a student of philosophy it is gratifying to me to recall the part philosophy has played in the emancipation and consequent development of this spirit, and I hope you will forgive me if I recall to your mind such names as Francis Bacon, Huxley, Spencer, J. S. Mill, to mention a few of the Englishmen alone, and to remind you of the efforts

they put forth to explain and defend this spirit and thus to help bring about the victory which we now assume as a matter of course.

Where the ordinary layman admires medicine only because it rids him of his aches and pains, the "philosophical" layman, in addition, *and as a philosopher or a student of philosophy*, admires medicine because of the scientific spirit by which it is inspired and directed. And this spirit has been most eloquently expressed in your meetings here. I know that laymen such as myself have found them a great source of inspiration, not only because of the painstaking research, the splendid results, and the faithful devotion to a task reported here, all of which are eloquent testimony to the scientific spirit of medicine, but also because of the fine fellowship of science expressed in your interest in one another's work, a fellowship most eloquently expressed in the splendid demonstrations of appreciation with which you have received the work of your distinguished guests and your distinguished members.

This good fellowship is such as to move a student of human affairs and human progress to regret that it is absent, in word or deed or in both, in so many other branches of human endeavor. We do not have it to this extent in philosophy unless all confess the same metaphysics, it is notoriously absent in politics, and the history of religion is sufficient evidence of its absence in this field. There is no record of a war fought between exponents of rival scientific theories. Opponents of science like to point out the fact that science has been used in war for pur-

poses of destruction. These critics should be reminded of the fact that on such occasions science has been employed in the name of ends supposedly nobler than the ends of science itself. It is such uses of science which strain the international fellowship of science, though only temporarily, after which the brotherhood returns at once to the common interest and the common purpose. This fellowship of science is a true expression of the common inter-

ests of man, we may even say, of the brotherhood of man, a phrase which we use so much but put so rarely into practice. It is a fellowship which is a happy by-product of devotion to the cause of science and to the scientific spirit and which might well take as its motto the words of Plato

“THE DISCOVERY OF THINGS  
AS THEY TRULY ARE IS A  
COMMON GOOD TO ALL MAN-  
KIND”

# Editorial

## MEDICAL OBSERVATIONS IN HAWAII

### II *The Early Manifestations of Leprosy*

The interest of the medical visitor to Honolulu turns naturally to leprosy, first of all, as the most advertised disease to be seen in the Islands. The tale of the leper is so bound up with the history and romance of Hawaii, from the time of the early missionaries and Father Damien down to the stories of Jack London, who certainly had a more accurate knowledge of the clinical aspects of leprosy than we might expect from a writer of fiction. To the average educated citizen of the United States the word Hawaii invariably suggests volcano, pine-apple, sugar cane, ukelele, surfing and leprosy. If we added anything more to this list it would probably be, interestingly enough, hula dancing and missionaries. The inevitable association of leprosy with Hawaii has an ironic tragic aspect, leprosy was not indigenous to the Islands, but, it is believed, was imported from China. In the Polynesian native race it apparently found a favoring soil, so that today, in spite of the large numbers of Chinese inhabitants, it is the native Hawaiian, or his hybrids, that constitutes the major portion of the sufferers from this infection. In Michigan I

had come into contact with about thirty cases of leprosy during the last twenty-five years, but with one exception these were all advanced cases, typical textbook pictures, of leonine facies, the one exception being a generalized tubercular type of the disease of several years duration. When one's acquaintance with leprosy is based upon the advanced form, he has, as I discovered in Honolulu, a very inaccurate and incomplete conception of this disease. Indeed, he cannot be said to know leprosy in its most active and virulent stage, the most important one as far as diagnosis is concerned. Through the most kind courtesy of Dr J T Wayson of the U S Public Health Service, I was given the opportunity of seeing at the Leper Receiving Station in Honolulu a wonderful clinical demonstration of the earliest manifestation of leprosy. There were about one hundred and seventy cases in this hospital at the time. The great majority of these were Hawaiians and part Hawaiians, a small number were Orientals, and only a few were Caucasians, Scotch, German, Scandinavian and American. To the station are sent all new and suspected cases for a confirmation of diagnosis, for preliminary observation and treatment, to be latter transferred to the Leper Colony on Molokai, should this be considered necessary. From the cases

at hand Dr Wayson selected individuals, or groups, showing the very earliest recognizable lesions in different stages of evolution and resolution, and the varying forms and degrees of pigmentation and depigmentation. This was a clinical demonstration of extraordinary interest and the pictures of the disease presented here were so new and striking, and so unexpected as cardinal features of its symptomatology, that it was like the discovery of a new disease entity. These early lesions of leprosy are not adequately presented in any textbook, to my knowledge, and some of the most striking ones are not mentioned anywhere in the literature of the disease. The clinical pictures drawn of leprosy in the current textbook articles are nearly all based upon the well-established and advanced stages of the affection, and give no hint of the wholly dissimilar lesions of the early stages. Yet it is in these early stages that the fight of the human organism against the progressive bacillary invasion is so strikingly shown. After one has seen a large collection of lepers and has studied them collectively, the old clinical classification of different forms of the disease, based largely upon the symptoms of pigmentations, anesthesia, nerve involvement, nodule-formation, etc., appear to be illogical and unnecessary, since all of these apparent varying forms are simply the result of degree of invasion, and are dependent almost wholly upon the progression of invasion and the individual susceptibility, rather than upon any special pathological character of

the individual case. There is no hard and fast line of demarcation between any of these chief symptoms of leprosy. They may all occur together at the same time, or may follow one another, at some time in his career the leprous patient will have experienced all of the type-symptoms or phases of the disease. It is misleading, therefore, to depict separate clinical and pathological types of leprosy as having any distinct entity. The disease should be regarded from the much broader standpoint of a progressive generalized invasion varying in time and degree in various localizations. From the old textbooks one also gets the idea that the development of leprosy is an extremely slow affair, extending over many years, and, therefore, that it is not likely to develop in childhood or early adult life. There were a number of young children in the Receiving Station at the time of my visit, and, if I remember correctly, Dr Wayson told me of a case of a leprous baby of eleven months of age. Moreover, the appearance of well-defined leprous lesions may be very sudden—a few months, a few weeks, even a few days, may be the history of individual cases. In one case seen by Dr Wayson the lesions had appeared only four days previously. In other cases the history may be that of a first crop of lesions seen many years ago, their complete disappearance for years, and then a sudden reappearance. These long spontaneous remissions are very disturbing in their possible relation to any supposed therapeutic effects. In one case seen at the sta-

tion, supposedly a recent acute invasion, a history was obtained of the occurrence of skin involvement of urticarial nature thirteen years previously, which Dr Wayson believes to have been the first clinical evidences of the infection in this patient. The early skin symptoms are of a surprising nature, and can easily be mistaken for a number of non-leprous conditions. One of the typical early lesions is the so-called "bee- or wasp-sting". It looks precisely like a bee-sting, a reddened, slightly swollen area with a central lighter point. They look also like mosquito bites or hives that have been slightly rubbed. Other lesions resemble ringworms so closely that errors in diagnosis may easily occur. All of the forms of mycotic dermatitis and pruritus show the same close clinical similarity. In the cases in which the first symptoms are quickly followed by a long period of remission the diagnosis of an acute exanthem, particularly measles, might be made. A differential diagnosis between early leprosy and syphilitic rashes may also be very difficult. The final proof is, of course, the bacillary demonstration, and no early case should be definitely decided as one of leprosy without the positive proof of the presence of acid-resisting bacilli in the skin lesions. The method employed at the Receiving Station is very much better than the usual biopsy excision of a section of skin which is fixed, imbedded and stained in sections for the bacilli. A small incision is made in the suspected cutaneous area with a sharp scalpel, the blade is slightly turned and with-

drawn scraping the side of the incision. The tissue juice, cells and blood thus obtained on the knife blade are spread on a slide, fixed by heat and stained as for tubercle bacilli. If it is a case of leprosy the bacilli in such a smear are numerous and easily seen. The procedure is much less unpleasant for the patient than the excision, the slight cut heals rapidly, and the diagnosis can be obtained almost immediately. In the suspected cases sent to the Receiving Station over 98 per cent of these bacillary tests have been positive on the first trial. I was very much impressed with the allergic character of these early skin manifestations, they resemble local allergic reactions more than anything else, and, I believe, will be found to be such. It is interesting that if the incision test is made after the local lesion has reached its height of intensity which it may do in several days, the tissue juice obtained contains great numbers of "beaded" bacilli or disintegrating forms. The implication would be that some degree of local bactericidal immunity had been attained. During their evolution the early cutaneous lesions are not painful, but are tender when pressed upon, there is a sensation of tension and more or less pruritus. There is also more or less fever and general malaise during the invasion stage. As the hyperemia and edema disappear, pigmentation or depigmentation follows, and a certain amount of anesthesia, usually in the older portion of the area involved. The pigmentations and depigmentations vary greatly in character and degree.

and can in themselves be very confusing clinically. They may appear as macules, or in large patches. In themselves they cannot be taken as having positive diagnostic value, but in any suspicious case should be tested by incision and bacillary examination. One of the most interesting color phenomena of the invasion stage of leprosy is a peculiar bluish tone of the skin of the forehead. It is seen best by oblique light, it is a peculiar gray-blue metallic shimmer beneath the epidermis, it reminds one of the blue-line of the gums in lead-poisoning, but is more diffuse. It suggests a very finely punctate cyanosis. It is mentioned by Jack London in his tale of the Islands, "The Sheriff of Kona" as "the darkening of the skin above both eyebrows, just like the dimmest touch of sunburn—but that there was a shine to it, such an invisible shine, like a little highlight seen for a moment and gone the next." Another of the early clinical signs of leprosy is the peculiar blob-like enlargement of the ear lobe. It suggests the swellings of the skin in myxedema, and microscopically shows a proliferating granulomatous inflammation of the stroma of a myxedematous nature. Great numbers of bacilli are present in this stroma. This involvement of the ear lobe is also mentioned by Jack London in "Koolau the Leper" as a "bloated ear-lobe" flapping "like a fan upon his shoulders," and in "The Sheriff of Kona" "Yet there it was, on his brow, on his ears—the slight puff of the earlobes." The cord-like thickenings of the nerve-trunk so strongly empha-

sized by various writers as an early diagnostic sign of leprosy, were seen in the ulnar nerve of only a few of the cases examined. In one boy the enlargement of the nerve trunk was very marked. Marked neurotrophic changes were seen in the hands of two children, one a boy of 10-12 years showing a marked degree of this condition, so that it must be rated among the early symptoms. All of the symptoms described above occur as the first ones, before any deforming granulomatous development takes place. They constitute a clinical picture of leprosy quite different from that usually given by the textbooks. Unless one has actually seen these early lesions it would be extremely easy to err in diagnosis, and this is of very great importance because of a recent announcement that in certain portions of the South indigenous cases of leprosy are now being discovered. Advanced cases are always turning up in the hospitals of our large cities, while these usually conform to the classical textbook pictures and are easily recognized, it is a question of some significance as to how many early cases there may be in the country that have not been recognized. As to the results of treatment with Chaulmooga oil and its derivatives it would be premature to make any definite statement. That under such therapy marked remissions of the disease occur there is no doubt, the condition of the patient may be so improved that an apparent clinical arrest or cure is indicated, and the patient may be returned to his home on parole. In such patients

relapses may unfortunately occur. The situation is very much the same as in the case of syphilis and tuberculosis, an apparent clinical cure—the reduction of an aggressive infection to a latent stage—may be obtained therapeutically. This for leprosy is a great advance, not only as far as the patient himself is concerned, but as far as the protection of the community is involved. It will take a generation, or several, before the full worth of the present treatment of leprosy can be evaluated. Nevertheless, the reduction of so many active lesions to latent ones must have an effect upon the spread of the disease, and in regions in which the treatment is vigorously pushed over a long period of time the number of lepers should diminish rather than increase. As to any influence of a concurrent syphilis upon the lesions of leprosy, or of a subsequent leprosy upon the course of syphilis no definite information was obtained. Some observers believe that syphilis is often more malignant in a leper, leading to earlier ulceration and mutilation, and more rapid development of the leprosy lesions. Other observers have not noticed any influence of either disease upon the other. Leprosy is a sinister infection. There is no recognizable local lesion of entrance of the infecting organism, as in the case of the primary chancre of syphilis. When the disease is recognized, no matter how early, it is already a generalized invasion. There is no therapy that will reduce the lesions of the disease quickly to a state of latency and clinical cure, as that of the arsenicals in the case of syphilis. The unpleas-

ant clinical aspects of leprosy, its more certain recurrences after periods of latency and its more inevitable course make it to the popular mind a much more-to-be-dreaded disease than syphilis. When added to this is the growing certainty that the infection may at times be quickly acquired under certain conditions of exposure, and develop with a relatively rapid incubation the popular dread of the disease is more than justified. The Receiving Station at Honolulu offers a great opportunity for intensive research and study of this disease. With the present laboratory equipment and the lack of sufficient staff and funds this investigation cannot be carried out in an ideal manner, and it seems a great opportunity lost. If the Federal or local Territorial Government cannot finance such a research laboratory, surely here is a wonderful opportunity for some of the multimillionaire missionary families to take up again the good work of their ancestors and found such a laboratory for the Study of Leprosy. The memorial fund in the honor of Leonard Wood to be used in a campaign against leprosy in the Philippine Islands is a wonderful thing and should have its counterpart movement in Hawaii. The Receiving Station in Honolulu is doing fine work under its present handicap, for the daily practical demands upon the staff are so great that the purely scientific study must take second place. To Dr. Wayson and the other members of his staff I wish here to express my appreciation and thanks for their most kind and instructive demonstration of their wonderful material.

## Abstracts

*The Pre-operative Treatment of Graves' Disease by a Combination of Iodized Fatty Acid and Vitamins A and D* By GILBERT L. ADAMSON, M.D., AND A. T. CAMERON, S.Sc., F.R.S.C. (The Canadian Medical Association Journal, October, 1928, p. 420)

Harvey, in 1927, had noted that cod-liver oil (which contains some iodine) when fed to goats, causes passage of more iodine into their milk than when the equivalent amounts of potassium iodide and olive oil are fed, from which an effect of some specific constituents of cod-liver oil on general iodine metabolism may perhaps be adduced. It was suggested by Dr. I. M. Rabinovitch that Lugol's solution might be replaced by a preparation of iodized jecoleic acid incorporated with a vitamin concentrate from cod-liver oil—a preparation to which the trade-name of Vitiodum (Forte) has been given. Good results have been reported in cases of Graves' diseases to whom this preparation was administered instead of Lugol's, by Dr. Rabinovitch and Dr. Mason of Montreal. With the approval and coöperation of the Medical Research Committee of the University of Manitoba, Adamson and Cameron have carried out a series of tests that are now sufficiently lengthy to justify preliminary report. Their results showed that this combination of iodized fatty acid and vitamins A and D is at least equivalent in value to Lugol's solution in the pre-surgical treatment of cases of Graves' disease, though as yet little light has been thrown upon the mechanism of its action. This seems to suggest a new and desirable field of investigation into normal and pathological thyroid function. Vitiodum (Forte) is stated by its manufacturers (Averst, McKenna and Harrison) to consist of a gelatine capsule containing 275 units of vitamin A (U.S.P. technique of measurements)

and not less than 75 units of vitamin D (as calculated by the non-official technique suggested by McCollum, Simmonds, Shipley and Park) together with iodized jecoleic acid in amount containing 0.03 available iodine, the equivalent of that present in 10 minims of Lugol's solution. These capsules dissolve in warm water liberating a greenish oil. No precipitate is given with silver nitrate, nor does the presence of acid liberate any iodine, so that the presence of iodide can be regarded as excluded. Analyzed by Kendall's procedure, figures for iodine content were found to vary from 0.02 to 0.03 gm., the lower figures being probably too low through the large amount of relatively volatile fat present. Jecoleic acid is an unsaturated acid of the type of oleic acid, with the formula  $C_{19}H_{30}O_2$  in which the position of the double bond does not appear to have as yet been definitely ascertained, so that its formula can be written at present  $CH_3(CH_2)_nCH=CH(CH_2)_nCOOH$ . Iodized jecoleic acid correspondingly is  $CH_3(CH_2)_nCHI=CHI(CH_2)_nCOOH$ . Because of the success of the pharmaceutical preparation in the first tests it was desirable to find out to which of the constituents the action was due. Accordingly tests were made on eleven patients using the vitamin fraction and the iodized fatty acid fraction. The tests in themselves are insufficient in number, but they suggest the strong probability that both the vitamin fraction and the iodized fatty acid fraction are necessary for definite effect. It remains to be determined whether both A and D or but one of them is necessary, and whether the iodized jecoleic acid can be satisfactorily replaced by iodides and other types of iodine compounds. From their series of cases the authors draw the following conclusions. Vitiodum, a combination of vitamins A and D and iodo-



fatty acid, is as effective as Lugol's solution when administered in Graves' disease, its beneficial action and the limits of its beneficial action closely resembling those of Lugol's solution. Vitiodum has not, in their experience, produced any gastro-intestinal disturbances during or following its administration. It is probable that neither the vitamins nor the iodo-fatty acid alone are effective. It is very desirable that further work be undertaken, not only to have records of a much larger number of cases accurately checked during vitiodum administration, but to investigate as widely as possible the relation between the vitamins concerned and thyroid and iodine metabolism.

*On the Occurrence of Blood Dyscrasias Following the Administration of Neoarsphenamine* By W. ROLAND KENNEDY, B. Sc., M.D. (The Canadian Medical Association Journal, October, 1928, p. 439)

Within the last decade medical literature has contained from time to time reports of reactions with unusual blood pictures following the use of arsenical preparations in the treatment of syphilis. The first reports of such blood dyscrasias were made by Leredde and Labbe and Langlois in 1919. Kennedy reports the development in a patient in the course of antiluetic treatment with neoarsphenamine, of a hemorrhagic diathesis with bleeding from the gums, epistaxis and hematuria. There was no antecedent history of a similar character in either family or personal history. Of particular interest were the blood findings, a much reduced platelet count, a prolongation of the bleeding time and non-retractility of the clot. With cessation of bleeding there was a rapid return to normal of the blood platelets and bleeding time. In short, there existed a toxic thrombopenic purpura or purpura hemorrhagica. A review of the literature supports the view that neoarsphenamine and sulpharsphenamine are the culpable preparations and not arsphenamine. The blood dyscrasias develop in a case of syphilis under treatment with arsenical preparations fall into three distinct clinical categories. Purpura,

purpura with hemorrhages and aplastic anemia with hemorrhagic diathesis. The purpuric-anemic syndrome may follow either intramuscular or intravenous injections. That neoarsphenamine and sulpharsphenamine exert a toxic action on the bone marrow has been generally accepted. The blood picture and the bone marrow lesions are similar to those of benzol poisoning. These arsenical preparations in short exert a direct destructive action on leukocytes, platelets and red blood cells. The interference with the platelets causes the hemorrhagic diathesis, and the leukopenia and anemia result from the toxic action on the other elements, the white and red cells. In neoarsphenamine there is a double benzol ring, and the benzol radical is probably responsible for the pathological process rather than any impurity in the drug, as has been assumed by some. The lesion, however, is rare. Prevention is the best remedy. The occurrence of mild nitritoid symptoms and slight purpuric lesions are a prodromal indication. Jaundice may also appear in like manner. In such cases arsphenamine and other antiluetic remedies can be safely used and should be substituted. As neoarsphenamine and sulpharsphenamine are arsenical preparations sodium thiosulphate intravenously is indicated in increasing doses from 0.15 to 0.6 gm. in 20 per cent aqueous solution daily. In cases that develop a progressive anemia reported blood transfusions have been life saving. These enable the patient to live while the toxin is being eliminated and the blood centers are thereby given a chance to regain their function. This process is usually slow except in young adults. It has been noted by Weil and Iseli-Wahl that with transfusions convalescence is often obtained without relapse, but that in pernicious anemia transfusions are of no ultimate benefit.

*The Epidemiology of Undulant (Relapsing) Fever in India* By A. V. HANNA (The Public Health Reports, Sept. 21, 1927, p. 2459)

From July 1, 1927 to June 30, 1928, 11 cases of undulant fever in India have been established in 13 cases. 30 cases

cases were diagnosed during April, May and June, 1928. The cases occurred sporadically and were widely scattered. Multiple cases in one locality are probably largely explained by a greater accuracy in diagnosis. In two instances two cases occurred in one family. In another, a farmer and an employee who worked together but lived separately both acquired the infection. Forty-six of the patients lived on the farm, seven in towns of less than 1,000, and twelve in towns with a population between 1,000 and 5,000. Of the remaining 18 cases, seven lived in towns of over 50,000 population. Sixteen occupational groups were included. 39 were farmers, 6 farmers' wives, 1 farmer's daughter, 6 packing house employees, 10 housewives not living on a farm, 4 students, 6 mechanics, 2 insurance agents, a dean of a college of law, a physician, an attorney, a nurse, druggist, veterinarian, merchant, bookbinder, buttermaker, a worker in an ice-cream plant, a fisherman and an imbecile. There were 63 males and 20 females. Two cases only were under 13 years of age—a boy of 7 and a girl of 8. The oldest patient was 73 years of age. The infrequency of the disease in the young and the concentration of cases in the age group 20-49 is most striking. In those cases having no contact with stock the absence of such a grouping is apparent. With three exceptions the infection was clearly acquired within the State. In only five cases had the patient taken any but local trips within one year, and in no case had they been traveling in Southern states or in foreign countries within recent years. A study of the diet of the patients was made as to the individual consumption of dairy products and meats. There were 52 cases in which the evidence indicated that the infection was acquired from cattle. In the study of the cattle suspected of being the source of these infections presumptive or suggestive histories of contagious abortion were given in 21 instances and confirmatory serological evidence was obtained. In 2 instances not even a suggestive history was elicited, but sera gave strong agglutination reaction. Another case was in a veterinarian who used raw milk

but who also was treating several herds of cattle for contagious abortion. In 8 additional cases it was clearly evident that the condition of contagious abortion was in the herds, but serological examinations were not made. In 18 cases the milk was regularly purchased from a public dairy supplying raw milk, while in 2 cases pasteurized milk was ordinarily used, although extra supplies of raw milk were purchased from local stores. Serological tests were not practicable where public dairies received milk from several sources. Histories of the herds, however, were procured, and in 15 instances the infection was known to be present in some of the herds. A second group included 11 cases in which the evidence indicated that the infections were acquired from hogs, 5 being packing-house workers and 6 farmers. In a third group of 4 cases there was a known possible source in both cattle and hogs. In one case only did the evidence strongly suggest that the infection was secondary to a previous human case, and this patient was one of the two fatalities that occurred. In 15 cases no clear evidence of the source of the infection could be obtained. The mode of transfer of the organism from the infected animal to man is a matter of great importance. In 25 cases the evidence suggested that the organism was transmitted through raw milk or cream. In the case of the packing-house workers, it may be accepted that the organism was acquired either from the infected meat or from excreta, and gained entrance through the injured or unbroken skin, or by way of the digestive tract. The same would hold good for the other cases in which the infection was acquired from hogs. In the remaining cases it was impossible to determine the precise mode of transfer, although there are two possibilities, either through dairy products used as food or by contamination with infectious excreta from livestock. It is evident that those working around stock are exposed more dangerously than those using the same dairy products but not working with stock. It seems evident that a goodly proportion of the infections were acquired from contamination by animal body discharges. The

possibility that the organism may gain entrance through the skin, either abraded or apparently normal, must be recognized. There was no evidence obtained from the Iowa cases that the infection was in any case acquired from goats, sheep or horses. The clinical symptoms of the Iowa cases showed a marked variation in symptomatology and physical findings, as is characteristic of this disease. The onset was usually insidious, but in a few instances was sudden. The first symptom usually is weakness, and this is the only constant one. The most striking feature of the disease is profuse night sweating, but this not always present. Sensations of chilliness were very common, and rigors occurred in the severe cases. General aching, headache, backache, and arthralgia accounted for most of the pain. Anorexia, succeeded by a good appetite, even in the presence of fever, was common. Constipation was the rule. Insomnia, irritability and apprehension was the usual nervous disturbances. Secondary bronchitis sometimes occurred. The patients often did not feel ill. In more than half of the cases no abnormal physical findings were detected, but a palpable spleen and epigastric tenderness were often noted. The temperature was irregular and intermittent, usually with morning remissions, often to normal. In less than one-third of the cases were there known undulations with periods of apyrexia. The total white count tended toward a slight leucopenia, the differential usually showed a decrease in polymorphonuclears with a corresponding increase in mononuclears. The course, which covered a period of three weeks to nine months, was marked by a progressive loss of weight and an

anemia. Arthritis, orchitis, mastitis and cardiac disturbances were infrequent complications. The case varied in severity from an ambulatory to a malignant type, but the intermittent form with relatively mild persistent symptoms was common. No case was included in which an agglutination of *Br melitensis* in a titer of at least 1:80 was not obtained. Of the 83 cases studied a higher titer than this was obtained in 78 (94 per cent). In 46 cases there was complete agglutination in a serum dilution of 1:1280 or higher, in 9 cases there was complete agglutination in the 1:5120 dilution. The agglutinins were repeatedly observed to increase during the course of the disease and slowly to decreased following convalescence. Bacteriological study could be made on only a few cases. In 9 patients *Br melitensis* was, however, isolated from the blood, and from five of the seven cases studied in hospitals the cultures were positive. The grouping of the organisms isolated from the patients has yet to be done. The prevention of the disease cannot be brought about wholly by the pasteurization of milk. The disease is also an occupational one in packing-house workers and in those handling stock. In these the prevention of the disease will be dependent upon the control of the infection in animals and in precautions taken on the part of those handling stock. In the packing house cases the disease is clearly an occupational one, these patients have been unable to work for a period varying from 1-5 months. For compensation to be obtained by workmen acquiring this infection it must be recognized that undulant fever among packing-house workers is an occupational disease.

## Reviews

*Blood and Urine Chemistry* By B H GRADWOHL, M D, Director of the Gradwohl Laboratories, St Louis, Mo, and IDA E. GRADWOHL, A B, Instructor in the Gradwohl School of Laboratory Technic, St. Louis, Mo 542 pages, 117 illustrations and 4 color plates The C V Mosby Company, St Louis, Missouri, 1928 Price in cloth, \$10.00

This volume is intended to be a textbook for laboratory workers and practitioners of medicine. The methods are set forth as clearly as possible, following the plan used by the authors in the instruction of laboratory technicians, and are standard and up to date. They are explained in detail so that the book may be a useful working manual in the laboratory, these explanations are given in simple style, the calculations in the proper form, and there is a full explanation of the apparatus required in the performance of these various tests. The book is divided into four parts. Part I, Technic of Blood Chemistry, Part II, Chemistry of Urine, Part III, The Interpretation of Blood Chemical Findings, and Part IV, Basal Metabolism. The methods given under these different sections are very complete and up-to-date. The authors emphasize the practical importance of blood chemical methods in both surgical and medical practice. There is hardly a specialty in medicine in which these methods are not of importance in the summing up of the individual's disability, as they touch upon the integrity of liver and kidney function, upon internal glandular secretory activity, upon operative risk, and upon all that goes with metabolic function and dysfunction. In the estimation of operative risks blood chemical tests have shown their great importance. This volume offers a most convenient compilation of all the most important chemical tests, and should be of service

to the laboratory worker. The book is well printed, is easily and conveniently read, and the illustrations, while adequate, are fair.

*The Conquest of Disease* By THURMAN B RICE, A M, M D, Assistant Professor of Sanitary Science, Indiana University School of Medicine 363 pages, 62 charts and figures. The MacMillan Company, New York, 1927 Price in cloth, \$2.50

The author states his purpose in writing this book to be "To set forth the most recent scientific information concerning the transmissible diseases to the end that these diseases may be controlled or perhaps ultimately eradicated." To make the subject interesting, if possible, to the general reader, and to such persons and students as may need to study the subject. The complete conquest of the transmissible diseases waits as much upon the intelligent appreciation of the facts by the laity, as it does upon the advances in research made by the medical profession, to emphasize the great advances that have already been made through scientific methods by comparing the past with the present. Confidence in the methods and motives of science is a most important asset to the people of the modern world, and in no field is its value more dearly demonstrated than in the conquest of disease. The discussions presented are accurate, based upon fact, and presented in simple, non-technical language. The expert can find no fault with this presentation of the victories of modern medical science over disease. The style is interesting and devoid of the hot-air or sophomoric vulgarity which has characterized other popular books of this kind. There is no attempt to be sensational, its pages are pervaded with a quiet decent sense of humor which places the book far ahead of such smartly attempts as DeKruif's

"Microbe Hunters" The romance of the fight against disease is presented in this volume more accurately than in the book just named, and with decency of treatment, without yellow-journalism appeal. Therefore, it is a book that should be read by all intelligent persons to whom the facts presented in it should become common knowledge and practically applied in daily life.

*The Principles of Anti-Natal and Post-Natal Child Hygiene.* By W. M. FLEDMAN, M.D., B.S., M.R.C.P. (Lond.), F.R.S. (Edm.). Senior Physician to St Mary's Hospital for Women and Children. 743 pages, 161 illustrations and 14 plates, including over 100 portraits. John Bale, Sons and Danielson, Ltd., London, 1927. Price in cloth, \$7.00.

This book is intended to be a companion volume to the author's book on "The Principles of Ante-Natal and Post-Natal Child Physiology," with which it is published uniform in size and manner of treatment. It is a fore-runner in this field of preventive paediatrics, comprehensive in its treatment, and should appeal to every educated and thoughtful person, lay or medical, who is more than superficially interested in the welfare of children during their various phases of ante-natal and post-natal life. The volume is also designed as a work of reference for paediatrists, medical child welfare workers, and students engaged in original investigations concerned with the hygiene of child life. The material of the book comprises three parts: Prolegomena, Ante-Natal and Post-Natal Hygiene. In Part I the historical survey of child hygiene contains much interesting subject matter drawn from many sources and all intelligent and educated readers will find this profitable reading. Its 63 pages constitute a very valuable monograph on this subject. It is illustrated with the portraits of those workers who have made some valuable contribution to the development of child-hygiene, including not only medical men and research workers, but social workers as well. For all of these this volume is of great value as a reference book and a useful guide, as it sum-

marizes critically and in considerable detail practically everything that has been accomplished in the various branches of Child Hygiene up to the time of publication. The biometrics of child hygiene, ante-natal and intra-natal mortality, child mortality and maternal mortality are fully discussed in Part I. In Part II, Heredity and Environment in their relation to child hygiene, the physiology of the fetus and the care of the expectant mother are given full attention. In Part III the physiology of early post-natal life, neo-natal hygiene, general nursery hygiene, the nutrition of the infant and the child, breast feeding, wet nursing, artificial feeding of infants and feeding of older children, clothing, muscular exercise, role of sunlight and its artificial substitutes, physiology and hygiene of the premature and congenitally debilitated infant, hygiene of the teeth and the sense organs, the prevention of infectious diseases, the physical and mental growth of the child, the mental hygiene of early life and adolescence of puberty form the chapter headings, and each of these subjects receives adequate treatment as far as our knowledge goes. The most important facts of modern research are given clearly and concisely, with full reference to the original papers. There are numerous valuable charts and figures. The material brought together in this book is of the utmost importance, and should be known to every intelligent parent. It can be easily understood by any educated layman, and is recommended to such. The book is well printed, and the illustrations adequate.

*A Textbook of Pharmacology and Therapeutics or The Action of Drugs on Health and Disease.* By ARTHUR R. CUSHNY, M.A., M.D., LL.D., F.R.S., Late Professor of Materia Medica and Pharmacology in the University of Edinburgh. Ninth Edition, Thoroughly Revised, by C. W. EDMUNDS, A.B., M.D., Professor of Materia Medica and Therapeutics in the University of Michigan, Ann Arbor, and J. A. GUNN, M.A., M.D., D.Sc., Professor of Pharmacology in the University of Oxford, Oxford, England. 743 pages, 73 illustrations. Lea

and Febiger, Philadelphia, 1928 Price in cloth, \$6.00

This classic work on the action of drugs and their applications in therapeutics had been constantly revised by Professor Cushny through eight editions. The rapid progress in experimental investigation and practical application in the field of therapeutics is strikingly shown in comparing these eight editions during the twenty-five years in which they appeared. In the eighth changes were made by Cushny in the chapters on digitalis and the cinchona bases, and on ergot. He also added new chapters on histamine action and the related symptoms of anaphylaxis and shock, and on the insulin treatment of diabetes, and on the vitamins. Changes were also made in the sections on cocaine, quinine, thyroid, strychnine and pituitary. These additions were compensated by the rearrangement and simplification of the chapters, and by the curtailment of the space given to obsolescent drugs. The text was also embellished with various references to drugs found in general literature. The immediate object of the present edition is to bring it in line with the tenth edition of the United States Pharmacopoeia, and the opportunity has been utilized to bring the subject matter also up to date. The present revision has endeavored to maintain the critical spirit which was such a valuable feature of the book, and, wherever possible, the original text has also been preserved. The work of the revising editors has been most successfully accomplished. They have succeeded in prolonging the active life of Cushny's most valuable book—it remains still the leading textbook in pharmacology and therapeutics, and it will continue to fulfill the important role played by the preceding eight editions in its critical sifting and promulgation of the advance of knowledge in this field. In accomplishing this successful revision the editors have paid an adequate tribute to the memory of the author, and have extended the great influence which he had in the field of experimental and didactic pharmacology.

B.S., Ph.D., Dr. P.H. Professor of Research Bacteriology in the Northwestern University Medical School, Chicago, Illinois, Third Edition, Thoroughly Revised 733 pages, 103 engravings and 8 plates. Lea and Febiger, Philadelphia, 1928. Price in cloth, \$7.00.

Many notable and significant contributions to bacteriology and related subjects have been made since the last edition of this book. Therefore, thorough revision, much rewriting and the introduction of much new material has been necessary. The present moment is a transitional one in bacteriology, it is becoming a new science in many ways, and it is not possible at the present time to make safe predictions as to the future. This book seems to have lagged behind somewhat in the new developments in the field of bacteriology. There is very little about bacterial dissociation in this work—in fact this term is not even in the index. It is rather an old-fashioned type of bacteriology that is presented here—the cataloguing of various species and forms, as to morphology, cultural characteristics and pathogenic qualities, but there is very little of the modern knowledge of bacterial metabolism, cycles, transmutation, and involution, etc. The Kahn test, Dick test, scarlet fever antitoxin, filterable viruses, bacteriophage, filtration, etc., have been considered in this edition, but of the newer work and problems of bacteriology there is very little mention. Mellon's important work is not even mentioned. The author seems to have turned a blind eye or a deaf ear to the modern problems of bacterial biology that in recent years have received so much attention and discussion. The book is well printed, in convenient reading form and legible type, and the illustrations are adequate. The book is really more adapted to laboratory work than as a textbook covering the teaching field of bacteriology. Practical diagnostic application is emphasized rather than critical scientific discussions of the many perplexing phenomena that have been observed in the field of bacteriological investigation and which remain to be correlated before the natural history of bacterial life becomes intelligible.

*Bacteriology, General, Pathological and Intestinal*. By ARTHUR ISAAC KENDALL,

# College News Notes

THIRTEENTH ANNUAL CLINICAL SESSION, APRIL 8-12, 1929

Dr Frank Bell Steele (Fellow), formerly of Salt Lake City, is now Medical Officer at the U S Veterans Hospital at Maywood, Illinois

Dr Stewart R Roberts (Fellow), Atlanta, Ga, has been made Chairman of a Committee to write the History of Medical Education in Georgia

Dr Ralph Kinsella (Fellow), has recently received the appointment as Professor of Internal Medicine of the St Louis University Medical School

Dr L R DeBuys (Fellow), New Orleans, La, has been elected President of the Louisiana State Pediatric Society for the present year

Dr I I Lemann (Fellow), New Orleans, La, is author of an article entitled "Nephritis in Children and Young Adults with Especial Reference to Focal Glomerulo-Nephritis," appearing in the September issue of the Southern Medical Journal

Dr Orlando H Petty (Fellow), Philadelphia, Pa, is author of a Handbook for the Patient, entitled "Diabetes, Its Treatment by Insulin and Diet," published by F A Davis Company This is the fourth revised and enlarged edition and contains an introductory foreword by Dr John B Deaver

Dr Frank P Norbury (Fellow), Jacksonville, Ill, addressed the Christian County Medical Society at Taylorville, July 19, on "Evolution in Diagnostic Methods"

Allen H Bunce (Fellow) and Dr Stewart R Roberts (Fellow) were among the principal speakers

Dr David J Davis (Fellow), Dean of Illinois School of Medicine, and Dr Julius H Hess (Fellow), Professor of Pediatrics at the same institution, are members of a Committee to "consider the present status of work on vaccination against tuberculosis with the Bacillus Calmette-Guérin, and especially the application of the method of vaccination to the general public by the Chicago Municipal Tuberculosis Sanitarium, where this organism has been studied by animal experimentation for about one year," according to the Journal of the American Medical Association

Dr Edwin C Ernst (Fellow), St. Louis, Mo, represented The Radiological Society of North America at the International Congress on Radiology at Stockholm, Sweden, during last July

Dr Albert Soiland (Fellow), Los Angeles, Calif, attended the International Congress on Radiology at Stockholm, Sweden, as a delegate from The American Radium Society

Dr B H Orndoff (Fellow), Chicago, Illinois, organized a party of sixty-seven American Radiologists, mostly from The Radiological Society of North America, to attend the International Congress on Radiology held at Stockholm, Sweden Dr Orndoff attended the Congress as a delegate from The American College of Radiology

At the Annual Meeting of the Eighth District Medical Association at Atlanta, Dr

Dr I S Trostler (Fellow), Chicago, Ill, addressed the Oneida-Forest-Village

County Medical Society at Rhinelander, Wisconsin, on August 3, on "Some of the Less Known Uses of Roentgenotherapy"

Dr Maximilian J Hubeny (Fellow), Chicago, Ill, presented "The Rôle of Roentgenology in Psychiatry" at the recent meeting of The American Roentgen Ray Society at Kansas City, Missouri

Dr John L. Chester (Fellow), Detroit, Mich, who is chief of the visiting staff at Eloise Hospital, Eloise, Mich, was recently appointed an attendant on medical service at Providence Hospital, Detroit. Dr Chester spoke before Michigan State Medical Society at Detroit on September 28th on "Electrocardiograms and Their Clinical Significance," having previously addressed Tri-County Medical Society at St Louis, Mich, September 6th, on the subject of "Rheumatic Heart Disease"

Dr George M Kober (Fellow), Washington, D C, retired as Dean of the Georgetown University School of Medicine, Washington, on September 18, after twenty-seven years' service. Dr Kober has been placed on the Board of Regents of the University and made Dean Emeritus of the Medical School. He is one of the founders of Georgetown Hospital, and was formerly President of the Association of American Medical Colleges and also of the Medical Association of the District of Columbia

The Graduate Department of the University of Michigan and the Michigan State Medical Society conducted postgraduate clinics at Grand Rapids, Flint and Jackson, Michigan, during October. Dr Martin A Mortensen, Battle Creek, Dr Frank Smithies, Chicago, Dr James D Bruce, Ann Arbor, and Dr Walter C Alvarez, Rochester, Minnesota, all Fellows of The College, were among the speakers at these postgraduate clinics

Dr James H Means (Fellow), Boston, and Dr Warfield T Longcope (Fellow), Baltimore, were among the speakers at a series of afternoon lectures sponsored by

the Medical School of Harvard University at Boston, during October

Dr J Gurney Taylor (Fellow), Milwaukee, was elected a delegate to the American Medical Association at the recent annual meeting of the State Medical Society of Wisconsin in Milwaukee

Dr George W F Rembert (Fellow), Jackson, addressed the Issaquena-Sharkey-Warren Counties Medical Society at Vicksburg, Miss, on the subject "Vincent's Infection of the Gums," on September 11

Dr Henry Boswell (Fellow), Sanatorium, Miss, Dr Felix J Underwood (Fellow), Jackson, Miss, and Dr L J Moorman (Fellow), Oklahoma City, Okla, addressed the Southern Tuberculosis Conference and Southern Sanatorium Association at Biloxi, Miss, September 12-15

Dr Solomon L. Cherry (Fellow), Clarksburg, W Va, addressed the Central West Virginia Medical Society, September 19, on "Medical and Dental Cooperation"

Dr Charles A Ray (Fellow), Charleston, W Va, past President of the State Medical Association of West Virginia, arranged the scientific program for the meeting of the Fayette County Medical Society at Charleston on August 14. Dr Arthur A Shawkey (Associate) spoke before the meeting on "Colic in Infants"

Dr Rock Sleyster (Fellow), Milwaukee, a member of the Board of Governors of The American College of Physicians and a member of the Board of Trustees of the American Medical Association, addressed the Eleventh Councilor District Society at Ashland, August 9, on "Psychiatry and the General Practitioner"

Dr Arthur R Elliott (Fellow), Chicago, was one of the speakers at the Third District Medical Society Meeting at Madison, Wisconsin, on October 12

Dr George Piness (Associate), Los Angeles, was made President-Elect of the



American Association for the Study of Allergy at Oakland, Calif. Dr. Ray M. Balyeat (Fellow), Oklahoma City, was elected Vice-President of the same Association.

At the Clinical Congress of The American College of Surgeons held in Boston, October 8-12, the following members of The American College of Physicians appeared on the program:

Dr. J. H. Means (Fellow) et al.,—Dry Clinic on "Demonstration of Methods of Treatment of Fractures, and Demonstration of Cases."

Dr. Henry A. Christian (Fellow),— "Missed Pedagogic Opportunities Incident to the Usual Organization of the Resident Medical Staff of the Hospital" and Dry Clinic on "Medical Diagnostic and Therapeutic Clinic."

Dr. Joseph C. Doane (Fellow), Philadelphia,— "Measuring the Professional Efficiency of the Hospital."

Dr. Josiah J. Moore (Fellow), Chicago,— "Relation of the Clinical Pathologist to the Medical Staff and the Scientific Work of the Hospital."

Dr. Franklin W. White (Fellow),—Dry Clinic on "Intussusception of the Bowel occurring within the Stomach following Gastro-enterostomy."

Dr. Myrtelle Canavan (Fellow), Curator of the Warren Museum, Harvard Medical School—Demonstrations.

Dr. Elliot P. Joslin (Fellow) et al.,—Dry Clinic on "The Treatment of Diabetic Feet."

Dr. Joseph H. Pratt (Fellow),—"Chronic Appendicitis, Differential Diagnosis."

Dr. Christopher G. Parnall (Fellow), Medical Director, Rochester General Hospital, Rochester, New York, was elected President-elect of the American Hospital Association at the annual meeting held in San Francisco August 6-10, 1928. Dr. Parnall was recently appointed consultant to the Sealy and Smith Foundation of Galveston, Texas, and also consultant to the Board of Health of the City of Indianapolis on the building program for several new units of the Indianapolis City Hospital.

The following are a few of the new publications for 1928 by Fellows of The American College of Physicians:

*Laennec, A Memoir*. By GERALD B. WEBB, M.D., President, Colorado School of Tuberculosis, Colorado Springs, U.S. Government Delegate to the Laennec Centenary, Paris, December, 1926. 146 pages, with 13 full page plates. New York: Paul B. Hoeber, Inc.

*Recent Advances in Chemistry in Relation to Medical Practice*. By W. McKIM MARRIOTT, B.S., M.D., Dean and Professor of Pediatrics, Washington University School of Medicine. 141 pages, illustrated. St. Louis: C.V. Mosby Company.

*General Therapeutics*. By BERNARD FANTUS, M.S., M.D., Associate Clinical Professor of Medicine, Rush College of the University of Chicago, Member, Revision Committee United States Pharmacopoeia and of National Formulary Revision Committee. Chicago: The Year Book Publishers.

*Rules for Recovery from Pulmonary Tuberculosis*. By LAWRASON BROWN, M.D. Fifth Edition. Thoroughly Revised, 244 pages. Philadelphia and New York: Lea & Febiger.

*Diabetic Manual for Patients*. By HENRY J. JOHN, M.A., M.D., Major, M.R.C., Director of the Diabetic Department and Laboratories of the Cleveland Clinic. 202 pages, illustrated. St. Louis: C.V. Mosby Company.

*The Treatment of Diabetes Mellitus*. By ELLIOTT P. JOSLIN, M.D. (Harvard), M.A. (Yale), Clinical Professor of Medicine, Harvard Medical School. Fourth Edition. Enlarged, revised and rewritten. 998 pages, illustrated. Philadelphia and New York: Lea & Febiger.

Dr. Allen H. Bunce (Fellow), as Secretary of the Medical Association of Georgia, is managing a package library service at the A. W. Calhoun Medical Library, Emory University, Atlanta, whereby members of the Association may obtain material on various subjects.

Dr Hugh S Cumming (Fellow), Surgeon-General of the U S Public Health Service, has been elected a corresponding member of the Royal Society of Medicine of Great Britain

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Dr George Harlan Wells (Fellow), Philadelphia, presented a paper on "Drugs as Antigens" before a symposium on chemotherapy at the Philadelphia County Medical Society on September 26. Dr Solomon Solis-Cohen (Fellow), Philadelphia, appeared on the program as a discussor, "From the Viewpoint of the Internist"

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At the annual meeting of the Gibson County (Tennessee) Medical Society at Trenton, Tenn, August 21, Dr W Calvert Chaney (Fellow), Memphis, read a paper on "Diagnosis of Diseases of the Thyroid," illustrated with slides, and Dr Henry Rudner (Fellow), also of Memphis, discussed "Vincent's Disease"

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Under the presidency of Dr George D Porter (Fellow), Toronto, the Canadian Public Health Association held its annual session in Winnipeg, October 11-13

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Dr Joseph C Doane (Fellow), Philadelphia, after fourteen years in various capacities with the Philadelphia General Hospital, severed his connection as Superintendent of that institution on October 1

to become Medical Director and Visiting Physician on the medical service of the Jewish Hospital

During Dr Doane's administration, many interesting and epochal changes have been brought about at the Philadelphia General Hospital. Only last December were the new buildings dedicated. These six new units, erected at a cost of about five million dollars, added twelve hundred and fifty beds to the hospital plant. There are total accommodations in all buildings for twenty-six hundred patients, the largest city institution in America.

Dr Doane, as the new Medical Director of the Jewish Hospital, has been making plans for the introduction of graduate teaching in this institution for the first time in its existence. He has expressed the hope of receiving graduate classes from the University of Pennsylvania into the wards of the Jewish Hospital for teaching purposes

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The Carpenter Lecture of the New York Academy of Medicine for 1928 was delivered by Dr Aldred Scott Warthin, at the Academy on October 1, on "The Pathology of the Aging Process"

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Dr Harlow Brooks spoke on "Angina Pectoris" before the Graduate Fortnight meeting at the New York Academy of Medicine October 11, 1928

## OBITUARIES

Dr Ralph Campbell (Fellow, February 14, 1920) died in Los Angeles, August 18, 1928, aged 61. He was a graduate of the Jefferson Medical College of Philadelphia, 1890, and did post-graduate study in Germany. Dr Campbell was, at one time, professor of Dermatology at the College of Medical Evangelists, Los Angeles, and was formerly Secretary and Chairman of the Section of Dermatology of the American Medical Association. From 1908 to 1909, he was a member of the House of Delegates of the same Association. During a residence in Chicago he had staff connections with Cook County, Henrotin and Polyclinic Hospitals. In Los Angeles he had been on the staff of the Los Angeles General and the White Memorial Hospitals. Besides being a Fellow of the American College of Physicians, he was a member of his county and state medical associations, a Fellow of the American Medical Association, and a member of the American Dermatological Association. Dr Campbell's pleasing personality had made him a host of friends who, with the members of his profession, mourn his passing.

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Dr Samuel W Welch (Fellow), Talladega, Alabama, died August 20, 1928, of cardio-vascular disease.

In the death of Dr Samuel W Welch, State Health Officer of Alabama, the American College of Physicians loses one of its most distinguished Fellows. Dr Welch was

born February 14, 1861, and received his collegiate education at Howard College, with the degree of B.S. in 1881. He graduated in medicine at the College of Physicians and Surgeons of Baltimore in 1893, and later did post-graduate work at Johns Hopkins and Columbia Universities. He was in general practice at Talladega, Alabama, for a number of years, but throughout his career was interested in public health, having been a member of the Alabama State Board of Health since 1903. He was elected State Health Officer of Alabama in 1917 and made a very remarkable record in the upbuilding of a most efficient state health department, so that Alabama's public health system is regarded as the best in the United States. As a result of appropriations secured by Dr Welch from the State Legislature, Alabama has the largest number of full county health units of any state in the Union, and within the next year each of the sixty-seven counties of Alabama will have a full-time health officer with a complete health unit.

Dr Welch received many honors at the hands of his professional confreres, having been President of the State Medical Association in Alabama, President of the Association of Health Authorities of North America, and had he lived, would probably have been elected President of the American Medical Association at its next meeting. He was also a member of the American Public Health Association and the Southern

Medical Association. He was elected a Fellow of The American College of Physicians on March 10, 1925, and has been an enthusiastic and helpful member since that time. Dr. Welch was the author of a large number of articles dealing with all phases of public health administration.

Dr. Welch served as State Chairman of the Committee on National Defense, Medical Section, during the World War, and was also Chairman of the National Malaria Commission. His death took place at Montgomery, Alabama, on September 20, 1928, following a brief illness, though for some months he had been known to have cardio-vascular disease.

(Furnished by Dr. Seale Harris,  
Governor for Alabama)

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"Dr. George Palmer McNaughton (Fellow, February 22, 1921), Chief of the Medical Department of the Jefferson Clinic and Diagnostic Hospital of Detroit, Michigan, died of heart disease on August 21, 1928, while on a vacation near Gladwin, Michigan.

Dr. McNaughton was born in Ottawa, Ontario, in 1878, and received his early education in Milwaukee. He graduated from Rush Medical School in 1900 and served for two

years as Resident Physician in Cook County Hospital. Dr. McNaughton became Chief of Internal Medicine at the Jefferson Clinic in 1919 and has participated actively in the development of that institution. Previously he enjoyed large practices in Sault Ste. Marie and later at Standish, Michigan. He served for five years as Attending Physician to St. Mary's Hospital, was Associate Professor of Medicine in the Detroit College of Medicine and Surgery, and Consultant in Internal Medicine and Chairman of the Executive Committee of the staff of Receiving Hospital. He was elected a Fellow of The American College of Physicians in 1921.

Aside from his ability as a clinician, he had a charming personality. His imposing physique, his joy of living, his cheery manner, his great heartedness made him friends everywhere and in every company. Genial and dignified, he was the embodiment of courtesy, and his widespread interests made him a delightful companion. A generous kindness characterized everything he did. There are few men who have as many friends. His death will make his colleagues, and the profession, the poorer by the loss of a personality always enthusiastic, considerate and kind."

## LIFE MEMBERS

The Constitution and By-Laws provide, "In lieu of annual dues a Master or Fellow may become a Life Member of The College upon the payment of \$500 in cash, or \$100 each year until \$500 has been paid. In case a member desires to pay for life membership by paying \$100 yearly for five years, his annual dues shall cease when he has made three annual payments of \$100 each."

Life membership, of course, includes waiver of all subsequent fees, full membership privileges for life, benefits of the Clinical Session and the receipt of all official publications of The College, including *ANNALS OF INTERNAL MEDICINE*. A wise provision of the By-Laws is that all moneys received for life membership in The College shall be added to the permanent endowment fund, the principal of which shall be held intact and invested in securities approved by the Board of Regents, while the income only shall be available for meeting current expenses of the organization.

The life membership movement deserves the highest commendation and offers a source for a permanent endowment for the perpetuation of the work of The College. More Fellows should be interested in seeking life membership. The present life members are

Lewellys F Barker	Baltimore, Md
Oscar Berghausen	Cincinnati, Ohio
Carl R Comstock	Saratoga Springs, N Y
Charles F Martin	Montreal, Que, Canada
Nels C Meling	Evanston, Ill
John Phillips	Cleveland, Ohio
Adolph Sachs	Omaha, Nebr
Frank Smithies	Chicago, Ill
Alfred Stengel	Philadelphia, Pa
Noxon Toomey	St Louis, Mo
M L Turner	Berwyn, Md
Alonzo H Waterman	Chicago, Ill
Bernard L Wyatt	Tucson, Ariz

## THE COLLEGE LIBRARY

Through the gifts of a considerable number of the members of The College, more than one hundred volumes have been added

to The College Library in the Executive Offices

All members of The College who are authors or co-authors of books are requested to present a copy to The College, in order that a complete collection of all the books our members have produced or to which they have contributed may be made.

Books sent to the Executive Offices of The College are immediately indexed with the names of the donor and the date of the gift.

## 1928 SUPPLEMENT TO YEAR BOOK

During the summer months, Mr Loveland, the Executive Secretary, and his staff prepared the Supplement to the 1927-28 Year Book, and distributed same to all members of The College in good standing.

The Board of Regents of The College has determined the policy of issuing a complete Year Book every two years. Inasmuch as the regular edition for 1927-28 was printed during the summer of 1927, this Supplement was issued only to include new members elected since the publication of the last Year Book. It is necessary, therefore, to use the Supplement along with the Year Book proper to have a complete directory of all members of The College. During 1929, it is anticipated a new complete edition of the Year Book will be issued.

The Executive Offices still have in stock available copies of both the Year Book and the Supplement for distribution to those who wish to place orders. Supplement \$5.00, postpaid, Year Book \$1.00, postpaid.

THIRTEENTH ANNUAL CLINICAL  
SESSION

of  
THE COLLEGE

Boston, Mass, April 8-12, 1929

Dr James H Means, General Chairman of Arrangements for the next Annual Clinical Session of The College at Boston, reports the following:

"The headquarters for the Boston meeting will be the Hotel Statler. The scientific sessions will be held in its ballroom in the afternoons and evenings. The pro

gram for the scientific session is well in hand and there are already promises from a very representative group of distinguished Internists from all over the United States and Canada, some Fellows of The College, others guests. One of the items that bids fair to be of especial interest is a symposium on deficiencies—deficiencies of all sorts to be considered as a class of agencies productive of acute and chronic disease on a par, for example, with infections. This will be opened by Dr George R Minot who will speak on some of the fundamental aspects of deficiencies. Dr Minot will be followed by Dr S Burt Wolbach who will speak on the pathology of deficiencies, by Dr Joseph Goldberger on pellagra, Dr Randolph West on pernicious anemia, and Dr Edward J Wood on sprue.

"Dr Benjamin White of the Massachusetts Department of Health will give an hour's lecture one of the evenings upon a critical review of sera and vaccines in the prophylaxis and treatment of disease, the idea being to give the Internist the last word on just where we stand on specific immunologic procedures.

"Dr Homer Swift has promised to speak briefly on rheumatic fever and Dr James B Murphy on cancer. We also find on the program many speakers bound to be very welcome to The College, such as Dr Lawrason Brown, Dr David Riesman, Dr J C Meakins, Dr L F Barker, Dr J B Herrick, and many others."

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# The Relationship of Operability and Hemoglobin Percentage in Carcinoma of the Stomach\*

By HOWARD R. HARTMAN, M.D., *Division of Medicine, The Mayo Clinic*, and  
THOMAS WILLIAM BROCKBANK, M.D., *Fellow in Neurology,*  
*The Mayo Foundation, Rochester, Minnesota*

IT is commonly known that anemia may accompany carcinoma in any region of the body, particularly if the malignancy is advanced or if the vital abdominal organs are involved. In malignancy of the gastrointestinal tract, anemia is probably most severe if carcinoma involves the stomach (1), but the changes in the blood in similar lesions in the proximal colon (1, 3) call for further investigation. That anemia, in the presence of carcinoma of the stomach, bears some relationship to the operability of the lesion is often implied by the internist as well as the surgeon. We have been unable to find in the literature conclusive evidence in favor of such a view.

Our investigation was undertaken to ascertain, if possible, any correlation between the degree of anemia and operability in carcinoma of the stomach. We studied two groups of cases. The first group consisted of 150 cases of carcinoma of the stomach in which the hemoglobin reading was 40 per cent or less, excluding all cases in which there was a

history of gross hemorrhage. The cases were divided into two subgroups, one of 100 cases, in which the lesion proved to be inoperable because of its size or situation, or because of metastasis, and fifty somewhat similar cases in which operation was considered advisable and resection was performed. The second group consisted of 411 cases observed in the same period, 271 inoperable cases and 140 operable cases of carcinoma of the stomach, not selected as to hemoglobin percentage.

## GROUP I CASES IN WHICH THE HEMOGLOBIN WAS 40 PER CENT OR LESS

An analysis of the cases in which the hemoglobin was 40 per cent or less was made because various surgeons decided arbitrarily that if the hemoglobin was below this figure the patient should not be operated on. It was hoped that factors other than the immediate risk, which could be readily corrected by transfusion, might be disclosed which would justify the decision not to operate. In other words, there was considerable doubt

\*Submitted for publication July 16, 1928



as to whether a low hemoglobin percentage in a given case of carcinoma of the stomach should be interpreted by the surgeon and internist not only in terms of immediate risk, but in terms of ultimate prognosis.

The size of the tumors encountered on exploration could not be compared in the operable and inoperable cases, because accurate measurements were taken only of the resected growths. The position of the growth in the operable cases was as follows: 80 per cent in the pyloric third, 10 per cent in the middle third, and 8 per cent in the pyloric and middle thirds. In the inoperable cases, 65 per cent of the growths were in the pyloric third, 8 per cent in the middle third, 14 per cent in the pyloric and middle thirds and 1 per cent in the fundus, in 12 per cent the situation was not stated. The fact that practically all the lesions, examined after abdominal section, were reported to have been in the distal end of the stomach is due to the selection of cases as determined by the roentgenogram. Exploration usually is not carried out when the roentgenogram shows that the carcinoma is in the fundus, because it is not possible to remove such a lesion satisfactorily, exceptions to this are rare.

Table 1 shows the situation and percentage distribution of the metastasis. In the operable cases (operable as far as gastric lesion was concerned) nearly all the metastatic growths were said to be "removable" except those in the liver and some of those in the pancreas. Consequently metastasis was not proved by microscopic section as is usual in resectable metastatic growths.

TABLE 1—CARCINOMA OF STOMACH (GROUP 1—150 cases)

Metastasis	Operable, Per Cent	Inoperable, Per Cent
Liver	100*	35.0
Mesentery	66.0	56.0
Pelvis		2.0
Pancreas	30.0	33.0
Peritoneum		3.0

\*Some of these were questionable

Certain other factors which may be considered contributory to the general condition were briefly summarized. In the operable cases the diet had been reduced in 70 per cent, vomiting was present in 54 per cent, and obstruction in 38 per cent. In the inoperable cases the diet had been reduced in 51 per cent, vomiting was present in 63 per cent, and obstruction in 52 per cent. In Table 2 the most

TABLE 2—MEANS OF AGE, DURATION OF SYMPTOMS, LOSS OF WEIGHT, BLOOD PRESSURE AND HEMOGLOBIN (GROUP 1)

Cases	Age, Years	Duration, Months	Loss of Weight, Pounds	Blood Pressure		Hemo- globin
				Systolic	Diastolic	
Operable	57.5 $\pm$ 0.7	9.12 $\pm$ 0.7	26.8 $\pm$ 1.5	125.1 $\pm$ 2.1	71.3 $\pm$ 1.1	34.0 $\pm$ 0.4
Inoperable	54.0 $\pm$ 0.7	8.70 $\pm$ 0.5	22.0 $\pm$ 1.0	122.8 $\pm$ 1.8	68.3 $\pm$ 0.9	32.5 $\pm$ 0.3

important remaining data in the two types are summarized. These mean figures are slightly higher in the operable cases in regard to all the factors considered, but it is questionable whether the difference is sufficient to be noteworthy. It is an enigma that here should be a slightly longer history and greater loss of weight in cases of resectable lesions than in cases of inoperable lesions. One would rather expect the reverse to be true. The difference of the means of the hemoglobin readings in the operable and inoperable groups of this series of cases, while numerically significant, is so small to have any clinical value. The hemoglobin percentages of the two types in the cases in which hemoglobin was 40 per cent or lower are shown graphically in Figure 1. The mean hemoglobin in the operable cases was 34 per cent, and in the inoperable 32.5 per cent.

#### GROUP 2 CASES NOT SELECTED AS TO HEMOGLOBIN PERCENTAGE

For comparison, the hemoglobin percentages in this group are compared in Figure 2. The groups are summarized in order chiefly to provide some definite record of the mean hemoglobin in all cases accepted for exploration, and surgically determined as operable or inoperable. The mean hemoglobin, 65.3 per cent, of the operable cases is slightly higher than that of the inoperable, 62.6 per cent. The percentages bear about the same relation to each other as those in Figure 1. It may be somewhat disconcerting to the clinician to find, as were presented (Figure 2) that there

is such a high percentage of inoperable cases in which the hemoglobin is comparatively high and a somewhat similar percentage of operable cases in which it is comparatively low. Smithies stated "Low hemoglobin percentages have relatively little value toward indicating the presence or absence of metastasis." We may almost paraphrase this, inversely, by saying that high hemoglobin percentages cannot be inferred as even a fair measure of operability. The blood destroying potentialities of the growth do not seem to be closely linked up with its complete surgical removability.

The average hemoglobin in 454 cases of carcinoma of the stomach was stated by Smithies as 64.3 per cent, by Osler and McCrae in fifty-two cases as 49.9 per cent, by Eisen in seventy-nine cases as 50 per cent, the mean in our group of 411 explored cases was 62.9 per cent.

#### COMMENT

There is little to choose in the second group between the 65.3 per cent of operable cases and the 62.6 per cent of the inoperable, and criticism could readily be leveled at the suggestion that these figures indicate a tendency for a slightly higher hemoglobin in the operable cases than in the inoperable. The clinician may make the best of this if he chooses. In the first group there is also found a tendency of the hemoglobin in the operable cases to range slightly higher. The fact that in many operable cases the hemoglobin is below 40 per cent is significant enough in itself.

It may be further concluded that for apparently the same period the hemoglobin below 40 per cent is not records of The Mayo Clinic show two in itself sufficient reason for a surgeon not to explore in a case of carcinoma of the stomach, even though cases of inoperable carcinoma of the stomach to one of operable, in which the hemoglobin was below 40 per cent

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# Chronic Appendicitis from the Viewpoint of an Internist\*

By HARRY WALD BETTMANN, M D, *Cincinnati*

THE literature on chronic appendicitis has continued to grow during the past ten years. It has finally established certain truths. One such truth is that chronic appendicitis is in no way to be confounded with recurrent appendicitis. Recurrent appendicitis at the time it is observed is in reality an attack of acute or subacute appendicitis. In general we know that the more nearly the clinical picture resembles an acute attack the more sure the diagnosis and the more certain the curative results of an operation. Per contra, we know that the more chronic the condition, the less typical the picture, the less certain is the diagnosis, the more dubious the result of an operation. Finally, we know that when there has been no history of a preceding attack of acute appendicitis, and when the main clinical symptom is distress in the right lower quadrant an operation is almost sure to be a clinical failure. If judged not by the pathologist's report but by clinical results the total number of operations for chronic appendicitis have disappointing results in 40% of the cases.

One would expect that the gradual dissemination of these facts would lessen steadily the number of opera-

tions undertaken for so-called chronic appendicitis. Such is not the case. On the contrary, all internists meet an ever increasing number of patients who have undergone a useless and often a harmful appendectomy. It is hard to suppress a feeling of irritation at this situation, especially when investigation reveals the fact that nearly 60% of the patients who have had an unsuccessful appendectomy, had received no adequate study before the operation was decided on. Often a history of indigestion and a poke in the right iliac region seemed sufficient to the surgeon to warrant an operation. Hertzler called attention to the deplorable damage which has been caused by a foolish epigram, viz., that epigastric distress associated with right iliac tenderness spells appendicitis. Hertzler also refers to an unfortunate example set by the American College of Surgeons which several years ago sent to the hospitals of the Country what it called "a model history of chronic appendicitis," and he adds that broadcasting such as this from high places does irreparable harm.

\*Read before the American College of Physicians, New Orleans Meeting, March 8, 1928

# THE MORTALITY AND MORBIDITY OF THE APPENDICITIS

At the outset it is important to correct a widely prevailing opinion that operations for so-called "chronic appendicitis" are both safe and harmless. This is far from the truth. Even in the hands of the best surgeons there is a certain unavoidable mortality and serious after-effects can not always be prevented. In the hands of the average surgeons the mortality mounts and the sequelae are correspondingly more numerous and more severe. Before the surgical section of the American Medical Association in 1925 (\*J A M A, Vol 85, No 12, Sept. 10, 1925, p 865) J. Shelton Horsley uttered a warning which is frequently repeated and often ignored: that none but a highly qualified abdominal surgeon should undertake an appendectomy. In the discussion A. J. Ochsner emphasized this point of view and said that it is a mistake to consider appendectomy a minor operation. In 1922 A. B. Cooke (\*J A M A, Feb 25, 1922) reported that in many communities, the family physician is willing to remove the appendix. I have heard of a physician in a neighboring county who limits his surgical efforts to tonsillectomies and appendectomies. Why not? The answer lies in the increasing mortality from appendicitis throughout the United States during the past 25 years. A. Murat Willis (\*The Mortality in Important Surgical Diseases Especially Appendicitis—Surg Gyn and Obst 1926, 42, p 318) calls attention to the astounding fact that the mortality in cases of gall-stones and appendicitis has mounted continuously from 1900

to 1922. From 1905 to 1921 the death rate from surgical diseases of the kidney diminished 11%, from pelvic diseases 26%. The death rate from gastro-intestinal ulcers increased 72%; from thyroid disease 250%, and from appendicitis almost 31%. The percentage of deaths from appendicitis per 100,000 population increased in every five-year period from 1901 to 1922, viz., from 1901-1905, 11 per 100,000; 1906-1910, 11.2; from 1911-1915, 12.1; from 1916-1919, 12.4; 1920, 13.1; 1921-1922, 14.4—an increase of 30.9% in 22 years. Willis suggests that the increased mortality may be due in part at least to operations by untrained surgeons. Fred C. Warnshus (\*Factors Influencing Appendicitis Mortality, J A M A 86, No 7 Feb 13, 1926) reports on the mortality attending operations for chronic appendicitis in 35 representative hospitals in eight North Central States. The mortality in 5,664 cases was 1.68%. Lakeside Hospital, Cleveland, had 8 deaths in 282 operations. Ford Hospital, Detroit, 15 deaths in 389 operations—a mortality respectively of 2.8 and 3.8%. Several hospitals reported no mortality.

Mortality statistics present only a small part of the story. Diagnostic errors are abundant. As every physician knows the appendix is removed in cases of kidney and ureteral stone, tabetic crises, tumors of the spinal cord, cancer of the sigmoid, pin worms, colitis, neurasthenia associated with visceroptosis, hernia, ovarian disease, to say nothing of diseases in the upper abdomen notably gallstones, duodenal and gastric ulcers. Recently I saw a patient who had a typical his-

tory of duodenal ulcer verified by the X-ray. The surgeon whom he consulted removed his appendix with the deliberate purpose of influencing the course of the duodenal ulcer. Twenty-five years ago a great American surgeon prophesied that the time would come when patients suffering from digestive disorders would go not to medical men but direct to the surgeon for help. The prophecy is fulfilled. The results are evident.

It is bad enough that nearly 2% die from the operation, that countless errors in diagnosis are made, that 40% of the operated patients remain unrelied. In addition, a fairly large proportion of the patients are made worse by the operation and some are invalided for life. Hugh Cabot stated eight years ago that no abdominal operation should be regarded as trivial, inasmuch as it may be the starting point of a train of symptoms difficult or impossible to allay. In neurasthenics, he says, an unnecessary operation may be a real catastrophe, definitely confirming the patients in their subconscious view of the physical reality of their complaints. Cabot further calls attention to the long drawn out convalescence after abdominal operations in certain individuals. In a study of 300 patients unsuccessfully operated on for chronic appendicitis, I found 35 or 11.6% who were made definitely worse by the operation. The most serious complication is adhesions of various types, involving the omentum, the ileum and the cecum. In one patient, five operations had been performed in vain in the hope of relieving dense post-operative adhesions, in another young girl three operations

were performed unsuccessfully and she had several years of severe invalidism.

There is one sequel of appendectomy which is far from uncommon but which has received little study and no adequate recognition. I refer to *ileac stasis*. From the study of many cases I am convinced that ileac stasis is a distinct clinical entity, that it has a fairly characteristic clinical history and that it can be recognized by appropriate X-ray observations. Under ordinary conditions of health a "barium dose" passes completely through the stomach and small intestine and is found in the cecum and colon within eight hours after administration. Rarely are ten hours required for this transit. In ileac stasis, barium can be demonstrated in the terminal ileum 12 to 14 hours after administration, and in severe cases even 24 or more hours later. As a routine we administer barium at 10 P. M., the following morning the patient eats a light breakfast and presents himself for examination at noon, i.e., 12 to 14 hours after the barium is swallowed. If we are not dealing with a case of pyloric obstruction or other gastric delay we expect to find the ileum empty at the noon examination. When the barium is still present in the ileum we speak of ileac stasis. It is not my purpose in this paper to discuss ileac stasis at length, (it will be the subject of a future paper) but I shall describe briefly its relation to appendectomy. As all of you are aware many patients seem to recover completely from their symptoms after an appendectomy only to suffer a relapse of all their preceding complaints some

in the course of a few weeks, a few even before they have left the hospital, but most between four and eight months after the operation. These patients suffer from gastric distress either immediately or several hours after meals, there is a sense of fullness, often sour eructations, sometimes vomiting.

*Protocol* Miss H M Aet 29  
 Attacks of appendicitis at the age of 7 and 12 years. Was well until 18, when she developed pain in right iliac region and leucorrhea. At 22 had appendectomy and curettage. The appendix was said to be kinked. While in the hospital began to have severe "gas pains" and has never been free of them. Almost daily immediately after meals has fulness, epigastric pressure, violent and frequent belching. Distress lasts one-half to one hour, occasional regurgitation of hot clear fluid. Much rumbling of gas in abdomen. Bowels fairly regular.

Examination reveals normal gastric secretion, negative X-ray findings in stomach and duodenum. Median incision. Tenderness in right iliac fossa, worse at McBurney's point. Ileac stasis 12 hours after taking barium.

*Protocol* Mrs I B Aet 24 6 years ago one ovary removed. 4 years ago uterine operation and appendectomy without special indication. One year later began to have pains in chest, a crowded feeling after meals, desire to belch and great discomfort after meals, sour eructations, often severe pains in lower abdomen. Married 8 years. No pregnancy. Lost 30 lbs in weight and is afraid to eat.

Examination Heart and lungs

normal. Median incision. No right iliac tenderness. Urine normal. Gastric juice over-acid. X-ray negative for stomach, gallbladder and duodenum. Ileac stasis, 6 inches of ileum full, 12 hours after barium. Dietetic treatment. Seven months later marked clinical improvement. Ileac stasis no longer demonstrable, on two subsequent tests.

Ileac stasis is often found in unoperated patients and may be dependent on many causes. It may be present in cases of cecal tuberculosis or malignancy and in benign cases is thought by many clinicians (erroneously I believe) to indicate colitis. The symptoms of ileac stasis often lead the surgeon to perform appendectomy, the stasis itself being overlooked. In such cases the persisting symptoms have no real connection with the operation and should not be charged to its account. In other cases, however, the stasis is the direct sequel and result of the operation itself.

#### CHRONIC APPENDICITIS AND THE X-RAY

The main cause of needless appendectomies is the "furor operandi" of ambitious surgeons. Their chief aid and abettor is the roentgenologist. In no other department of roentgenology is there so much confusion and misunderstanding. As a result, the assembled literature on the X-ray of the appendix presents a fantastic mixture.

John B Deaver (*Surg Clin of N A*, 1925, v p 1515) says that the diagnosis of chronic appendicitis by the X-ray may be of use but it makes no appeal to him. Carman's disdain of the X-ray diagnosis of appendicitis

is well known and he treated the whole subject sarcastically in his classical textbook

In 1924 D Rappaport demonstrated to the Vienna Medical Society a series of X-ray plates and photographs demonstrating the filling of the appendix by the radiographic meal (\*J A M A, May 24, 1924, p 1708) Rappaport believes that the filling of the appendix is always pathological Non-filling of the appendix does not prove it to be normal Should the appendix retain its contents 24 to 36 hours appendectomy is justified The retention may be the only symptom of disease *before clinical signs of mischief become manifest* (Italics mine) Eight years ago Dr E H Skinner declared quite definitely that the filling of an appendix in an adult over 30 years of age proves that appendix to be abnormal F H Baetjer (\*Tice Practice of Medicine, Vol 7, chapter 6) says that six hours after a barium meal the cecum is fairly filled and the appendix under palpation will probably fill The frequency of visualization varies according to the several authorities from 35 to 90% On the next page Baetjer adds that he does not believe that every visualized appendix is necessarily pathological Putting these two statements together we learn that Baetjer does not consider 35 to 90% of all appendices necessarily pathological

Sidney Lange thinks the non-filling of the appendix a sign of probable disease Arens and Bloom (\*The Normal and Pathological Appendix Radiology, Dec, 1925) say that the appendix which fills readily during a barium enema is pathological They state that the absence of pathological changes

at an operation does not exonerate that organ, as symptoms may be caused by abnormal physiological reactions Apparently nothing exonerates the appendix Apparently also the arrow of the roentgenologists points north, east, south and west at the same time Crohn advises us to disregard entirely the filling or the non-filling of the appendix Many other conflicting references could be cited We are told by other roentgenologists that tenderness over the site of the appendix is the best sign of disease Levyn (\*N Y Med J, 1923, Vol 117, p 688) states that 75% of all appendices diseased or normal can be visualized But tenderness plus invisibility speaks for disease Sheridan (\*W M Sheridan X-Ray Findings in Patients with Chronic Appendicitis The Radiological Review, Dec, 1927) also says that tenderness in the appendiceal region is the chief sign of chronic appendicitis If the cecum fills it is not necessary to see the appendix, its position can be presumed It might be embarrassing to ask about those cases in which tenderness persists after appendectomy—fully one third of the total number

Could there be a more chaotic state of knowledge or rather can we speak of knowledge where so much contradiction exists? What shall we say of indications for operation based on observations so conflicting?

I have in my case records scores of reports from competent roentgenologists, whose conclusions in no respect corresponded with the conditions found at operation It is a fact that certain findings noted on one examination (visibility or invisibility, irregularity of filling, kinks and fixation)



may not be verified on subsequent examinations. If filling of the appendix is a sign of disease (Rappaport, Skinner) and non-filling a sign of disease (Lange) what appendix is normal? It is easy to reduce the whole subject of the roentgenological diagnosis of the appendix to an absurdity—an absurdity, however, with infinite potentiality for harm.

A few examples of X-ray reports

- (1) L S, June 12, 1925. Appendix outline very irregular suggesting chronic inflammatory changes. Same patient, Nov 17, 1926. Appendix visible, mobile, uniformly filled, not tender. Normal.
- (2) Report by a roentgenologist of national reputation. Miss S, age 40 years. The X-ray examination would suggest the presence of a gall bladder lesion associated with a bad appendix. There is, however, a marked curvature and rotation of the lumbar spine which might also play a part in producing pain.
- (3) M K, age 44, April 1923. Appendix irregularly filled, adherent, slightly tender. Patient has had absolutely no digestive trouble from 1923 to date.
- (4) Report by a leading roentgenologist, 1924. "Mr M K, age 50. Gastric hyperperistalsis, which is usually a reflex from a lesion beyond the stomach. Duodenal cap quite small and irregular, indicating either a spasm of the duodenum or an ulcer. Appendix outline distinctly visible, segmented, shows constrictions in its lumen. The above observation

could indicate the presence of chronic inflammatory changes about the appendix which might cause the spasm of the duodenum and reflex stomach symptoms. On the other hand, there might be a duodenal erosion or ulcer present. It might be advisable to test this out by putting the patient on a diet for duodenal ulcer. If he does not improve this would indicate that the contraction of the duodenum was due to a reflex spasm and that the cause of his symptoms was a bad appendix."

In defense of this roentgenologist it might be added that his examination antedated the Graham-Cole test. The patient was found to have gall stones with typical colic attacks and jaundice.

This from the leading roentgenologist in a community of more than 500,000 inhabitants!

#### THE SIMULATION OF CHRONIC APPENDICITIS BY ENTEROSPASM AND BY INTERCOSTAL OR COSTO-LUMBAR NEURALGIA

An article by H P Hawkins, appearing in the British Medical Journal Jan 13th, 1906, p 65, has never attracted the attention it deserves. Hawkins discusses the mimicry of appendicitis by spasm of the colon. He says that every physician learns in years of private practice that there is much abdominal pain which has no name and does not kill. He reports 35 cases of enterospasm, in eleven of which the appendix was removed without relief. The pains occur in both men and women in early adult life,

the patients are usually neurasthenic or neurotic, there is no evidence of organic disease, and in many cases the pains recur on and off for many years, the pains are usually referred to the right or left iliac fossa, there is no fever at any time, mucus may be passed in the stools, there are tangible evidences of colon spasm either by palpation or by inspection during an operation. Hawkins calls attention to the cord-like contraction of the colon recognizable by palpation. These cases have many points of resemblance to well defined types of spastic constipation described in most text-books. James T Case (\*A Roentgenologic Study of pain in the right lower abdomen — Northwest Medicine Vol xx, No 7, July 1921) in a characteristically lucid and instructive paper discusses his observations on patients who continue to suffer right iliac pain after appendectomy. He reviewed the history of all patients who in a given two months' period passed through the Roentgen Department of the Battle Creek Sanitarium, one fourth of these patients had undergone an appendectomy. In the absence of acute attacks or definitely recurring attacks almost every patient complained of a continuance of the pains and discomforts previously experienced, Case came to the conclusion that in a large percentage of instances of right lower quadrant pain the cause will be found in the distal colon, often in the pelvic colon and rectum. Among the common causes he mentions functional spasm, adhesions of the pelvic loop, the pressure of pelvic tumors, carcinoma, diverticulitis, hemorrhoids, fissures, rec-

tal ulcers and proctitis. He adds that enterospasm may be the expression of irritation through the central or sympathetic nervous system, or of simple colitis. In this connection it might be interesting to recall an article by J F Erdman and R F Carter (\*Malignancies of the Colon, Ohio State M J, Dec 1921) in which they refer to five cases of cancer of the colon which had been operated on for appendicitis, the cancer having been overlooked.

It has been only within the past few years that serious attention has been called to the fact that neuralgic states of the inter-costal and costolumbar nerves may give rise to symptoms which closely mimic intra-abdominal diseases, especially cholecystitis and appendicitis. Every practitioner of experience must recall cases in which the lancinating pre-herpetic pains of herpes zoster on the right side led him to suspect the presence of cholecystitis or other inflammatory disease within the abdomen. A few years ago Professor Strecker of Breslau (\*Deutsche Med Woch, 1926 No 4, p 150, Die Kneifschmerzhaftigkeit der Bauchhaut als diagnostisches Merkmal) declared that rheumatic-neuralgic disorders of the abdominal wall are extraordinarily frequent. He devised what he called a pinch-test to differentiate over-sensitiveness of the abdominal wall from intra-abdominal diseases. R von den Velden (ibid) says that circumscribed sensitiveness of the abdominal wall is not always to be interpreted as a projection of diseases of intra-abdominal organs. On the contrary he finds this tenderness of the wall very common in pri-

tients who have already been operated on for ulcer, appendicitis, gall stones, and gynecological conditions Boas described in 1926 (\*N Y Med J and Record, Jan 6, 1926) a method of distinguishing hyperalgesia of the skin from visceral disease. He applies Bier suction cups for one half hour twice daily to the sensitive area for 3-4 days. This will cause neuralgia of the skin to disappear, whereas deep tenderness remains. In this country, important pioneer work has been done by Dr J B Carnett of Philadelphia (\*J B Carnett Inter-costal Neuralgia as a Cause of abdominal pain and tenderness. Surgery Gyn and Obs., May 1926, pp 625-632), Chronic Pseudo-appendicitis due to Intercostal Neuralgia, Am J Med Sc, Nov 1927, p 579. Acute and Recurrent Pseudo-appendicitis due to Intercostal Neuralgia, Am J Med Sc, Dec 1927, p 833). Carnett is fully aware of the vast number of useless operations for what he calls pseudo-appendicitis, but adds that *the voluminous literature does not give any definite method by which preoperative differentiation can be made between true and false appendicitis*. Carnett proposes to supply a simple and yet dependable method of differentiation. He finds that the commonest cause of pain and tenderness in the right lower abdomen is found in the abdominal wall itself and not within the abdomen. At the outset he rejects in toto the elaborate theory of MacKenzie, Head and others that skin hyperesthesia is due to a visceroparietal sensory reflex. He says that "proponents of the visceroparietal reflex confine their attention to the

abdominal area of tenderness and do not seem to realize that the evidence of nerve irritability very commonly extends high up on the chest and is very often bilateral. Carnett finds it impossible to believe that a mild chronic appendicitis or any other visceral lesion could give rise to such a wide-spread 'overflow' visceroparietal reflex." I am inclined to believe that most clinicians will agree with him. Carnett's method of differentiating visceral from parietal tenderness is based on palpating the abdominal wall when the patient's muscles are alternately relaxed and tensed. "Tenderness which is elicited over relaxed muscles may be either parietal or of intra-abdominal origin. If the sensitivity remains when the muscles are firmly tensed the pain is parietal. Tenderness present with relaxed muscles and absent over tensed muscles is due to the subparietal lesion and its cause should be sought inside the abdomen." Carnett fortifies his views with elaborate studies of and diagrams illustrating the distribution of the intercostal and lumbar nerves and presents a convincing array of anatomical and clinical material. I am not familiar enough with the application of Carnett's methods to pass judgment upon them but from recent experiences and observations I am convinced that he has devised a most useful method of studying the subject and has made a real forward step. Every physician and surgeon should familiarize himself with Carnett's views which promise to clarify a dark field and may prove to be of epoch-making value.

We are thus advancing towards an understanding of right iliac pain. Essential enterospasm, enterospasm from lesions in the distal colon, recto-sigmoid and rectum, and finally costolumbar neuralgia are all actual clinical entities. In addition, we now have an important study in the pathology of chronic appendicitis from the Lenox Hill Hospital. \*(G. L. Rohdenberg. So-called Chronic Appendicitis. Archives of Path and Lab Med June 1927). Dr. G. L. Rohdenberg\* has studied 3214 appendices, of which 1374 showed chronic changes or what he prefers to call productive inflammation, beginning with infiltration of the submucosa with round cells and ending in fibrosis. The first changes occur near the tip and consist of infiltration of round cells about the Meissner ganglia; this process increases until the ganglia may be completely buried in round cells. The cells gradually decrease as fibrosis proceeds until the ganglia are found embedded in dense scar tissue. Corresponding changes are sometimes found in the ganglia in the neck of the gallbladder. Rohdenberg concludes that so-called chronic appendicitis is due to a lesion of the sympathetic nervous system, the lesion is not restricted to the appendix alone but is probably general

to the splanchnic system. The nerve lesions would explain reflex gastric symptoms, the attacks of spasm and pain. They also explain why removing the appendix or gall bladder or both does not always relieve the symptoms. Rohdenberg calls attention to one more important fact, viz., that chronic or productive changes do not markedly increase the liability of the appendix to fall a prey to severe acute inflammation. This corresponds to our clinical observation that the chronic sufferers are not more likely than others to have acute suppurative processes. One final word—and this a plea for a more prolonged and careful study of the individual patient. One of the serious shortcomings of our present medical and surgical methods is the quick diagnosis. Patients present themselves at group clinics or hospitals or appear before consultants for a so-called clinical survey and expect a decision in a few days or in a week. Nothing is more certain than that a quick decision cannot and should not be given in a very large percentage of our chronic patients. Quick decisions are often little more than clinical guesses, often very foolish ones. The well being of our patients depends in the long run on conscientious and prolonged observation.

# Specific Prophylactic Measures in Varicella and Measles<sup>\*†</sup>

By JEAN V COOKE, M D, *St Louis*

EFFECTIVE specific protection against communicable disease has been developed in smallpox, diphtheria and typhoid fever, in each case based upon different immunologic principles. In other common infections, efforts along similar lines have resulted in far less regular results. In some, although some reports are distinctly favorable, the lack of constant effectiveness has prevented the general use of such methods as have been advised, in others, there are practical difficulties in applying the protective therapy. Under certain conditions, however, the results of a given specific infection are of such known severity, that one is eager to use any prophylactic measure which offers even a moderate promise of protection. Chicken-pox and measles are two infections in which our knowledge of specific protective therapy is as yet incomplete. One is the mildest of the contagions of young children, and the other one of the most serious. Together they share the distinction of the greatest communicability of the exanthemata, with consequent rapidly spreading epidemics, and of being of unknown etiology. Little or no natural immunity exists to either except in early infancy, and, like the other common contagious diseases of child-

hood, their usual portal of entry is probably the upper respiratory tract. A brief discussion of the clinical value of the methods of protective therapy which have been used against these two infections is the object of this paper.

*Varicella* Since chicken-pox is such a mild infection, one might question the necessity for any vigorous attempt at prophylaxis. The instances in which the disease has been accompanied by serious complications are so extremely rare that they do not constitute a valid reason for the general use of specific protective measures. In institutions, however, the infection once introduced frequently spreads rapidly and may necessitate a prolonged period of quarantine. Also the danger of secondary infection of the lesions in weak and debilitated infants, and the discomfort caused in children wearing casts, makes prophylaxis highly desirable at certain times.

Two methods of specific protection have been used, one, the inoculation

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<sup>†</sup>Read before the American College of Physicians, New Orleans, Clinical Week, March 7, 1928.

of the contents of a varicella vesicle into the skin of a normal child, as suggested by Kling in 1913, to produce an active immunity. This is analogous to the now discarded method of "variolization" in smallpox and might be termed "varicellization." It is accompanied at times by the production of a mild localized lesion at the point of inoculation with apparently sufficient general reaction to cause immunity. Other children similarly inoculated after exposure show no local lesion but are protected from the clinical infection, and Hess and Unger have reported effective protection from the intravenous injection of small amounts of vesicle fluid in all except one of a series of thirty-eight infants. In typical successful "takes" by this method there develops, during the second week after inoculation, a papule, which passes through the same stages of vesicle and crust formation seen in varicella lesions, and which may leave a superficial scar. As in the case of smallpox, some of the children inoculated have developed mild generalized eruptions in addition to the local lesion at the point of inoculation. It has been the

experience of one observer (Hotzen) that the inoculation of normal infants not previously exposed to the disease, has been followed in a considerable number of instances by clinical chicken-pox. Such an apparent transfer of the infection by this procedure, however, has not been noted in our own cases, or generally by others in inoculation of those previously exposed.

The fluid for inoculation is collected after cleansing the surface of a fresh vesicle, by puncture with a sterile capillary tube. The inoculations may be made by application of the fluid to an area of scarification from a lancet or Pirquet chisel, by needle punctures, or by intradermal injection. During the first three days after exposure seems to be the optimum time for inoculation.

The results of most of the published reports have been that a rather large proportion of infants and children so inoculated after exposure to the infection, have failed to develop clinical varicella. A summary, (Table 1) for example, of six representative reports from Europe and Amer-

TABLE 1.—PROTECTION OF CHILDREN EXPOSED TO VARICELLA OBSERVED AFTER VACCINATION

Observer	Exposed Children Vaccinated	Developed Varicella	Exposed Children Unvaccinated	Developed Varicella
Kling	58	6	64	44
Handrick	127	45		
Rabinoff	96	6	142	114
Michael	32	7		
Greenthal	36	1		
Meyer-Stromfeldt	20	0		
Total	350	74 (20%)	206	158 (77%)

ica shows that of a total of 369 exposed children thus inoculated 72, or 20 per cent, developed varicella. Two of the observers include control groups of exposed uninoculated children in which 158, or 77 per cent, of 206 children developed the infection. The duration of this variety of immunity is uncertain, since some inoculated children have developed the infection after a later exposure.

On three occasions when a child developed varicella in one of our wards, we have inoculated the other patients on the same floor intradermally with diluted vesicle fluid. In each instance no further case developed among the twelve to twenty children so inoculated. These were all infants under two years of age. On another occasion in which varicella appeared in a ward of older children and similar intradermal injections of diluted vesicle fluid were given to twelve children, two of those inoculated developed chicken-pox. The question of the intimacy of exposure of such contacts is never certain, but without prophylactic inoculations, we have observed a much higher incidence of cross infections than the foregoing.

One of the chief difficulties in attempting this type of protective vaccination is in the securing of sufficient amount of vesicle fluid. Usually this material is obtainable in only small quantities even when several fresh varicella rashes are available. It is, consequently, necessary to dilute the fluid considerably with sterile salt solution in order to inoculate a number of children. Although in our own experience the apparent effect of "varicellization" in preventing the spread of a ward infection has in some instances been striking, in others we have felt that the lack of complete success might be attributed to the small amount of vesicle fluid which we were able to obtain for use. It seems likely that this factor may have some importance in the variation in protection noted by different observers. The results leave little doubt that the clinical immunity following such inoculation is in many cases attributable to the procedure.

A second method used in varicella prophylaxis has been the injection of contacts with small amounts of serum from children in the third week of convalescence from the disease.

TABLE 2—PROTECTION OF CHILDREN EXPOSED TO VARICELLA OBSERVED AFTER GIVING CONVALESCENT SERUM

Observer	Children Exposed to Varicella, Given Convalescent Serum	Amount of Serum Given cc	Children Developing Varicella
Blackfan and others	42	5	7
Schmidt	6	1 5-8	6
Weech	9	3-4 5	1
Mitchell and Ravenel	68	2-10	3
v Barabás	42	10-15	5
Total	167		22 (13%)

The serum has been injected intramuscularly and apparently is more effective if given during the first few days after exposure. Fewer observations have been recorded of the protective effect of this procedure but a summary (Table 2) of the five series in the literature shows that of a total of 167 exposed infants given from 15 to 15 cc of convalescents' serum, only 22, or 13 per cent, developed varicella. When available, amounts of 5 cc or more of serum would seem to offer more assurance of protection. The immunity, like that of passive transfer of antibodies in other infections, is temporary, and can be assumed to last only a few weeks. In a few instances in which infants given convalescents' serum developed chicken-pox, the incubation time was longer than three weeks. Apparently, definite protection to varicella is afforded in a considerable percentage of children given convalescents' serum within a few days of their exposure to the infection.

*Measles* The chief justification for the energetic use of any available prophylactic measures in measles lies in the considerable menace to life which this infection carries for young children. Although a disease of relatively little danger in itself, it is accompanied by a greatly increased susceptibility of the lungs to secondary infection with pyogenic cocci, especially streptococci. More than ninety per cent of the deaths in measles are due to a secondary broncho-pneumonia, and about three-fourths of these occur in children under three years of age. Although not a specific prophylactic

measure, one cannot help emphasizing the necessity of precautions directed toward the prevention of pneumonia in children suffering from measles. It seems certain that in the majority of cases, the organisms causing the secondary infection are acquired from a healthy carrier who comes in contact with the patient. To the fact that such carriers are more numerous among the personnel of a hospital staff is probably attributable the high incidence of secondary broncho-pneumonia among young children in institutions during epidemics. Although the measles-pneumonia mortality of 20 to 30 per cent, common among hospital children under three years of age during such epidemics, is very much greater than that noted in private homes, the potential menace of all contacts should be constantly in mind. A strict quarantine has probably its greatest value in protecting the patient himself from such a complication.

In general, specific measles prophylaxis is especially indicated only in infants and young children, since the methods now available make it practically impossible to protect children of school age who are subject to repeated and unsuspected exposures during an epidemic. Children in institutions, those who are ill with acute or chronic disease, and especially those with known tuberculous infection, should also be protected by specific measures whenever possible.

A few attempts at active immunization against measles have been made at various times using virus-containing material obtained from the upper respiratory mucosa or blood from patients in the pre-eruptive or early erup-



tive stages of the infection. These have not yet proved of practical value.

The value of serums obtained from the immunization of horses by streptococci isolated from measles in prophylaxis, is still to be decided. The only serum of this type commercially available during the past year has proved quite inert in preventing the development of measles in exposed children.

At the present time the only effective method in the specific prophylaxis of measles is in the intramuscular use of human convalescents' serum. Since the original employment of this procedure in the prevention of measles by Nicolle and Conseil in 1918, numerous reports verifying its effectiveness have appeared. Its success as a prophylactic measure is so universally accepted that the use of the method has become almost a routine in many places. It will suffice to review briefly the procedure advised and the results which can be anticipated from our own experience and that of many other observers.

Although modified by several factors, the results have shown that almost 90 per cent of children given convalescents' serum during the first week after exposure have failed to develop the infection. In a large proportion of those in whom measles appeared, the disease was of a mild or abortive type. In those given the serum after the first week of the incubation period, the appearance of the disease has been little influenced, although many cases have been of a modified, mild variety. In general it is apparent that the sooner after exposure the serum is given, the greater the likelihood of

complete protection, since the percentage of measles increases rapidly in those injected later than the 5th day. The modified measles observed in certain children given prophylactic serum late, or in insufficient amount, is characterized by slight or moderate fever which lasts only one or two days, by the mildness or complete absence of upper respiratory symptoms, by the rarity of a complicating bronchopneumonia, and by the changed and transient character of the rash. The latter is frequently of irregular distribution and the individual lesions are dwarfed and atypical. Indeed, the rash often would not be identified as measles without the attendant history.

The duration of the passive immunity to measles from convalescents' serum is temporary and can be relied upon for only a few weeks. Those who develop the modified disease after serum has been given, however, are probably protected permanently. For this reason, and on account of the relative freedom from complications in these milder infections, it would seem advisable often to administer serum even later than the first few days after exposure, in the effort to lessen the severity of the infection.

The optimum time during convalescence for collecting the serum for prophylactic use is thought to be approximately a week after the temperature has become normal. It is of course impossible to determine the measles-antibody titer of serum, and it seems probable that the potency in different individuals varies. For this reason it would be expected that pooled serums from several persons would have a more consistent pro-

protective action than that from a single individual. In some of the larger cities, in which measles is endemic, the health authorities have limited amounts of pooled serum available to physicians. The serum, if kept sterile, retains its immunological potency for a number of months. When it is not possible to obtain blood from an individual who is recently convalescent, the serum from persons who have recovered from measles several months or even several years previously may be used. In such instances, the antibody content is much lower than that of more recent convalescents and the serum must be used in considerably larger amounts. Even with larger doses, however, such serums are far less efficient in prophylaxis than serums from recent convalescents. A Wassermann reaction should be performed on serum before its use unless given to another member of the same family. Under conditions which make separation and preservation of serum difficult, whole blood may be used instead. This may be injected intramus-

cularly immediately after collection, before clotting takes place, or somewhat more readily when the blood is citrated to prevent coagulation.

The dosage of human immune serum employed is quite arbitrary on account of the lack of any method of determining its potency. It has been found that from 2 to 4 c.c. is usually sufficient to protect infants under three years of age if given during the first four days after exposure. Twice this amount is advised for children during the next two days of the incubation period, and 7 to 8 c.c. if given later. As has been previously mentioned, the best results are obtained when the prophylactic dose is given early after the contact.

The specific prophylactic measures at present available both in varicella and measles, therefore, have a considerable degree of effectiveness. Although at times they are applied with some difficulty, there are certain circumstances in which their use is of great value.

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# The Etiology of Erysipelas\*

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THE clinical history of erysipelas, when studied in combination with the pathological and bacteriological investigations expended on this disease, embraces almost every stage in the evolutionary progress of the art and science of medicine. Although the written history of this disease bridges the span of time from Hippocrates (about 430 B C ) to the present moment, nevertheless, it is only sixty years ago that Vulpian (1868) accurately described the histopathological picture and that Nepveu (1870) suggested in positive terms the parasitical nature of erysipelas.

In his "Epidemion" Book III, Hippocrates made the first written record of an epidemic of erysipelas, in words at once beautifully descriptive and adequately comprehensive, to the extent that the modern medical student may recognize therein the various stages observable in the idiopathic as well as traumatic forms of this disease. Unfortunately, the "Father of Medicine" confused erysipelas with many acute inflammatory lesions of the skin, subcutaneous tissue, and internal organs. Hippocrates believed that erysipelas was caused by bilio-sanguinary poisons occasioned by atmospheric and telluric changes. The celebrated physician, Celsus, under the reign of Augustus

and Tiberius, recognized erysipelas as a characteristic disease known to arise idiopathically without any apparent external abrasion, as well as in traumatic wounds. Galen (A D 130-301) clearly differentiated between phlegmonous inflammation of the deeper tissues and erysipelas of the skin and subcutaneous tissue.

The bilio-sanguinary origin of the disease, suggested by Hippocrates, became a tradition firmly believed in by the Arabian physician Avicenna and Ali Abbas, the Salernian physicians Ruggiero, Rolando and Guido de Chauliac. Even in the latter part of the 18th century the eminent Heister and Tissot adhered to this tradition. For a few centuries during the darkest of the middle ages, erysipelas was subjected to sacerdotal embellishment and extra-mundane forces shared honors with bilio-sanguinary poisons in the causation of erysipelas. Paracelsus (1491-1541) openly declared that the disease was caused by evil spirits and the revolt of angels within the victimized body. For a brief period witchcraft and astrology held sway and history relates of many unfor-

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fortunate sufferers with erysipelas who were persecuted for being possessed with the devil, or the "Evil Eye," and these victims were drowned, hanged or burned

With the advent of histo-pathological methods of study inaugurated by Morgagni (1682-1771) erysipelas was subjected to its first scientific study. In connecting the pathological lesions with the symptoms and signs of the disease during life, a large group of investigators headed by Platner, Sauvages and Pinel, the actual localization of erysipelas was attempted by histo-pathological studies. Thus it was that Callisen in 1734 stated that the disease affected the skin, subcutaneous tissue, muscles and blood-vessels within the area circumscribed by the erysipelatous margin. It was not until 1868, however, that Vulpian demonstrated beyond any reasonable doubt that the edematous congestion of the skin and underlying tissues in the erysipelatous lesion is mainly due to penetration into these tissues of large, finely granular leucocytes which uniformly penetrate the area involved in the lesion. Renault in 1874 confirmed adequately the thesis of Vulpian and made the important observation that as a rule only the lymphatic vessels are involved in the disease processes and that no definite changes are to be seen in the blood-vessels. It was Renault who suggested that erysipelas ends by resolution.

Toward the end of the 18th century the Hippocratic tradition of the bilio-sanguinary causation of erysipelas came in for its final death-blow. In England John Hunter and Gregory advocated the contagious nature of the

disease. On the Continent Lorry, Piorry, Velpeau and Trousseau wrote extensively on the infectious nature of this malady and in 1869 Volkmann emphatically wrote that "erysipelas is a wound-infection directly dependent upon the destructive activity of peculiar poisons produced in wounds by pathogenic bacteria. This prophetic outburst became a fact when in 1870 Nepveu described the presence of micrococci in the erysipelatous lesions and the blood of such patients. Nepveu erroneously described these organisms as "delicately oval-shaped, rapidly movable and variable in size." Orth in 1873 was more ingenious in that he accurately observed "micrococci in chain-formation in the contents of the erysipelatous bullae." By applying these micrococci to the skin of rabbits, Orth produced typical erysipelas lesions, from which he re-isolated or at least detected the original chain-forming micrococci.

Bitter contentions arose about the bacterial origin of erysipelas and it is difficult to understand how such eminent authorities and investigators as Lukomsky, Billroth, Ehrlich, Tillmanns and Wolff, and others, should have discountenanced the *a priori* relationship of these chain-forming micrococci to erysipelas. On the contrary, these men advocated that the micrococci were not the actual cause of the disease, but that they were carriers of the poisonous, non-organized substances from without to the inflamed areas.

With the advent on the scene of Robert Koch and his discovery of the solid nutrient culture medium, Fehleisen in 1881 fulfilled all the post-

ulates laid down by Koch and proved that the *Streptococcus erysipelatis* was the indubitable cause of erysipelas. Besides isolating this organism from every case of the disease studied, Fehleisen reproduced the disease with the pure culture both in rabbits and in man. The dramatic import of Fehleisen's attempt to cure neoplastic growths by superimposing on the same experimentally produced erysipelas, at least in seven humans, loomed high when he noted that slight retrogression of the tumor took place in some of these patients. This practice must have fallen into disrepute by unfortunate accidents, not reported in literature, for little or nothing was subsequently heard on this subject.

Since the discovery by Fehleisen of the *Streptococcus erysipelatis*, a great deal of controversy resulted in a state of confusion about the etiology of erysipelas, repercussions of which are heard in many recent studies bearing upon the specificity and non-specificity of Fehleisen's organism. Rosenbach in 1884 and Passet in 1885 believed that all streptococci isolated from a variety of pyogenic human infections were identical. Widal, Petruschky and Mamorek failed to distinguish between the streptococci isolated from puerperal sepsis and erysipelas. Bonome, Jochmann, Reiche and Schomerus and many others reported the isolation of staphylococci from erysipelas. Neufeld and von Leube not only isolated pneumococci from the erysipelatous lesions, but they also reproduced erysipelas in rabbits with these organisms. During this period no definite advance was made from the lines laid down by Fehleisen and

consequently it became necessary to develop new methods of biological study of the large group of hemolytic streptococci associated with pyogenic infections of man.

Classification of hemolytic streptococci by means of morphology and cultural characteristics failed to reveal any existing group or type specificities. Reactions of these streptococci on blood-agar or by sugar fermentation fell short of revealing unusual characteristics. The recent development of serological methods so successfully employed in demonstration of type specificities within the groups of typhoid-paratyphoid-dysentery-colon bacilli rapidly found their usefulness when applied to the *Streptococcus hemolyticus*.

By means of the opsonic index Wright and Douglas had already observed that during the acute attack of furunculosis and sycosis, the opsonins rapidly diminished in the patient's blood-serum. By treating such patients with staphylococcic vaccine a notable increase of opsonins took place. Ruediger in 1906 observed the same phenomenon in erysipelas patients. These studies had more than theoretical significance in that they suggested a preventive measure and possible cure of infectious disease. Schorer in 1907, Tunnicliff in 1908 and 1920, and Boughton in 1910 reported that by means of opsonification, specificities were detectable in scarlet fever and erysipelas streptococci. Similar results were reported by employing the complement fixation reaction. By making use of the precipitin reaction most authors claimed that the hemolytic streptococci formed

a homogeneous group and that classification of types of streptococci was not available by this method. Rose now in 1926, however, reported specific precipitin reactions in the diagnosis of scarlet fever, poliomyelitis, erysipelas and other conditions due to streptococcic infections.

The most hopeful method of classification of hemolytic streptococci was found in the agglutination, agglutinin absorption and animal protection tests. Although these methods were first employed by Van de Velde in 1898, it was not until 1919 that the streptococci were subjected to an extensive scrutiny by the comprehensive studies of Dochez, Avery and Lancefield. These authors discarded the use of cultural characteristics, bile solubility, hemolysis and sugar fermentations reactions, since such methods failed to reveal indisputable specific characteristics among groups of hemolytic organisms. By means of the agglutination, absorption and animal protection, these investigators observed four biological types of hemolytic streptococci during an epidemic of bronchopneumonia secondary to measles. This important study was followed by Havens in 1919 who found by the same methods that 93 per cent of 292 heterogeneous strains of hemolytic streptococci fell into 3 definite serological types. In rapid succession followed the most revolutionizing studies bearing upon the specificity of the scarlet fever streptococcus. Notable work on this discovery was contributed by Bliss, Tunnichliff, Dochez, Stevens, Gordon and the Dicks. By the combined efforts of these investigators, and in particular the distinguished con-

tributions by Dochez and the Dicks, it has been proven with a great deal of certainty that the *Streptococcus scarlatinae* is the cause of scarlet fever.

Aside from the brief study in 1920 by Tunnichliff on the agglutination of hemolytic streptococci from erysipelas, the question of specificity of these organisms had not been faced seriously. In reviewing the subject of the bacteriology of erysipelas, Birkhaug in 1924 was able to demonstrate that from a large series of hemolytic streptococci isolated from erysipelas sources, more than 90 per cent of these constituted a highly specific type of micro-organism, differentiable by means of agglutination, absorption and protection tests from scarlet fever streptococci as well as many heterogeneous strains of streptococci. He also learned that experimental erysipelas invariably follows the application of these virulent organisms to the skin of susceptible rabbits and that immune erysipelas serum would protect susceptible animals against localized erysipelas and septicemia induced by the intravenous inoculation of fatal doses of *Streptococcus erysipelatis*. In 1925 Birkhaug was able to demonstrate that a toxin was produced by the erysipelas streptococci, which when injected intradermally in susceptible persons elicited positive reactions similar in nature to the Schick and Dick tests. An identical toxin was found to be circulating in the patient's blood-serum during the early stages of erysipelas, only to disappear during convalescence. At that time the patient's blood-serum was found to contain an antitoxic principle, which in proper mixtures with the *Streptococcus cry-*

*syphilitis* toxin, completely neutralized the effects of the latter substance. These studies pointed directly to the possibility of producing a curative erysipelas antitoxin.

Eagles in 1924 and 1926, and Stevens and Dochez in 1926 corroborated the agglutination findings of Tunncliffe and Birkhaug. These investigators detected a slight antigenic relationship between the scarlet fever and erysipelas streptococci. Stevens and Dochez concluded that "the erysipelas strains form a closely related group of hemolytic streptococci. Scarlatinal strains form an equally compact group. The two groups are related antigenically but less closely related than the strains within the groups. These groups are related to pyogenic strains, but less closely than they are related to each other."

Eagles and Andrews working in

scarlatinal sera, but were completely neutralized with sera prepared with erysipelas strains. On the whole these studies corroborated Birkhaug's thesis of an apparent specific type of erysipelas streptococcus and toxic filtrate.

For the production of an erysipelas antitoxin, Birkhaug employed a deer and horse. After a consistent regimen of active immunization of those animals for about one year, the serum pooled from these immunized animals was found to possess a high concentration of antitoxic and antibacterial substances, which after careful animal experimentation, warranted its employment in human erysipelas.

In 1926 Birkhaug reported the therapeutic records of 60 patients treated specifically with the erysipelas antitoxin. The average dose of the unconcentrated antitoxin was 100 cc.

within 12 to 18 hours following the injection of the antitoxin

Musser in 1927 reported on the value of the erysipelas antitoxin treatment in eleven cases, noting the identical drop in temperature and pulse and disappearance of toxic depression following the antitoxin administration. Symmers and Lewis in September 1927 reviewed the 15,277 cases of erysipelas which had passed through Bellevue Hospital, New York, during the past 15 years. Previous to the antitoxin treatment almost every conceivable form of treatment was practiced and none of them appeared appreciably to shorten the course of the disease. These authors report 131 cases treated by the antitoxin method and conclude "As a result of the antitoxin treatment, the mortality in erysipelas was reduced from 10.1 per cent to 5.3 per cent, the patient's period of disability was reduced by slightly more than 50 per cent. This therapeutic benefit permitted a reduction in the nursing staff to the extent of about 60 per cent and effected a notable saving of bed linen and sleeping garments by doing away with the destructive effects of ointments and similar local applications. The antitoxin treatment of erysipelas marks an advance, the results of which are commensurate with those obtained in the treatment of diphtheria. As far as the immediate attack is concerned, erysipelas is now a vanquished disease."

Plato, Schultz and Collins in December 1927 reported observations based on 155 cases of erysipelas, of which 35 were treated with local applications, 80 with X-ray irradiation, 30

with erysipelas antitoxin, and 10 with X-ray and erysipelas antitoxin combined. The erysipelas antitoxin caused the return to normal of temperature and pulse and subsidence of symptoms in 2.3 to 3.8 days, as compared with 3.4 to 8 days in the control group. These authors also observed that the mortality among the antitoxin treated patients was one fourth of that recorded in the control series.

Allan in February 1928 reported from the Mayo Clinic 209 cases of erysipelas, 43 of which were treated with the erysipelas antitoxin method. His conclusions are essentially those of other observers and he mentions that mortality was reduced from 13.5 per cent among control series to 2.3 per cent among the antitoxin treated patients.

Blackfan, in a personal communication, in 1927, reported the antitoxin results among infants afflicted with erysipelas and concluded that "the streptococcus erysipelas antitoxin acts specifically in the treatment of young infants with erysipelas and is comparable to the use of antitoxin in scarlet fever, but if delayed until complications have developed, it is apparently ineffective."

Birkhaug has observed the antitoxin treatment in 36 cases of erysipelas in infants ranging in ages from two weeks to twenty-four months. The results obtained confirm the original thesis. Among the 36 treated infants 5 died from frank erysipelas and complications. Bearing in mind the extremely high mortality among infants afflicted with erysipelas, particularly under two years of age, it is safe to state that the erysipelas antitoxin



method has somewhat changed the grave prognosis of this disease

Finally, Birkhaug in 1926 attempted to develop methods for the prevention of recurrent erysipelas in such unfortunate individuals who suffer repeatedly with gradually severer forms of the disease. After a long series of studies, he finally observed that the period of active immunity following the last attack of habitual erysipelas patients was very brief. By injecting repeatedly once or twice a week 10 skin test doses of the erysipelas streptococcic toxin under the skin of these persons, it was observed that almost co-incidentally with the advent of positive skin response, the repeated attack of the disease took place. Following the course adopted in scarlet fever prevention, Birkhaug injected persons suffering with repeated attacks of erysipelas with 500, 5,000 and 50,000 skin test doses of the erysipelas streptococcic toxin, ten days being allowed to intervene between each subcutaneous injection. In order to increase the active immunity, recent patients have been injected with two additional doses of 100,000 and 250,000 skin test doses. At the end of the course of active immunization, the blood-serum of these patients is tested for its antitoxic content. In some of these individuals, 1 cc of the blood-serum was able to neutralize as high as 1000 skin test doses of the erysipelas streptococcic toxin. Already 68 persons with definite histories of recurrent attacks of erysipelas every fourth to twelfth week for a number of years, have

been immunized by means of the toxin. These persons, with only one exception have been free from recurrent attacks of the disease during a period exceeding two years.

### CONCLUSION

One notes with a great deal of interest that through the entire history of events associated with the clinical, anatomical, bacteriological and immunological studies of erysipelas, there runs an unbroken cord which unites the most ancient medicine with our present-day enviable state of medical knowledge. From the enormous literature that has accumulated on this subject alone, the author firmly believes that it conduces to precision and clearness to regard the *Streptococcus erysipelatis* as the true agent of this infection. The many data, when viewed both pro and con, bear the unmistakable marks of specificity, no longer aprioristic, but based upon careful observation and experimentation.

If the generous tribute to this work, offered by Symmers and Lewis, remains henceforth true that "the anti-toxin treatment of erysipelas marks an advance, the results of which are commensurate with those obtained in the treatment of diphtheria," and further, that "as far as the immediate attack is concerned, erysipelas is now a vanquished disease," then the medical profession should be grateful that a just reward has come at last to the large host of investigators who, not singly but unitedly, made possible the unravelling of the specific facts known today about the etiology of erysipelas.

# The Relation of Organic Brain Disease to Epilepsy\*

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IT IS obvious that a complete consideration of this subject cannot be condensed into a paper to which such a short time is allotted but a discussion of some important debated points will be given. The author has elsewhere given a more complete account of the etiology of epilepsy but important additions to our knowledge have been made since that time (Block (1), (2))

Convulsions occur from many brain diseases such as brain tumor, abscess, cysts, maldevelopment of the brain, porencephalia, cerebral hemorrhage, hydrocephalus, cerebral syphilis, arteriosclerosis, localized edema of the brain, traumata, fractures of the skull, meningitis, meningo-encephalitis, adhesions of the meninges, calcified echinococcus cysts, hypertrophy of the brain, agenesis cerebri, hypertrophic tuberous sclerosis, encephalitis, hydrocephalus, etc. This is at least a sufficient number to indicate the importance of intracranial lesions, at the same time, many raise the point that these are not in reality essential epilepsy, properly speaking, and yet many of them go through life with the clinical evidences and diagnosis of epilepsy. Thom and Southard (3) out of 205 autopsies on epileptics found

129 abnormal looking brains. Of the remaining 76, 8 had leptomeningitis. After deducting all cases with mental symptoms, only 8 cases were left which might properly be accepted for a study of idiopathic epilepsy, and 4 of these had organic evidences such as facial paralysis, etc. Munson (4) in 305 brain examinations (at Craig Colony for Epileptics) found that 179 showed some gross lesions, 100 showed some minor changes, and 26 were reported negative. The most common lesions were hemiatrophy, sclerosis in one temporal lobe, and ventricular dilatation, aside from hydrocephalus and meningeal thickening. Birth injuries and encephalitis played a role in the production of the brain lesions.

From a clinical standpoint Block found evidences of organic brain disease in 16% (of 200 cases studied), such as early encephalitis, cerebral hemorrhage, a unilateral difference in reflexes or muscular strength. This of course does not include organic brain diseases in which any other diagnosis than epilepsy was justifiable. Both a morphological and physiological asymmetry in the brain, as well

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as the rest of the body, is the rule rather than the exception and a post convulsive Babinski reflex has been found by Jellinek (5), Redlich (6), Quensel (7) and Serag (8) and others. Practically all writers find some degenerative changes in the nerve elements and sclerotic changes in the cerebral cortex in the microscopic study of the brains of epileptics. The interpretation of these findings have been quite different with different writers. Some claim they are the underlying causative factor, while others maintain they are the effect of the repeated epileptic attacks, because they are most marked in old long standing cases.

On the other hand, Osnato (9) says "I am quite certain that epilepsy is not a brain disease, that is, that the disease could not be explained by investigation inside the skull alone. I have carefully studied fifty seven cases of epilepsy and found that in only three were there any objective neurological signs. Two of these cases showed sensory motor types of cortical disturbances. They were traumatic cases with craniocerebral injury. The other case was one of so-called idiopathic type and showed a Babinski sign on one side and a sixth nerve involvement on the other.

Even Focher (10) who studied the asymmetry of Weber's tactile sensibility and found his test positive in 31/5% in 19 epileptics, came to the conclusion that it was the result of the epileptic attacks, as the longer the disease has existed the more frequently present the sign, two thirds of the positive results being after the epilepsy had existed for more than five years.

One-sided symptoms and signs are quite common in epilepsy aside from any evidence that a focal brain lesion exists, such as the difference in muscular contractions, the posture, deviation of the face and eyes, etc., during the attacks, unilateral difference in the abdominal reflexes, the unilateral Babinski reflex following a convulsion, or the difference in the length of time that the normal plantar reflexes take to return after a convulsion. Here again the question arises as to whether these differences are due to a physiological asymmetry (the contractions of the strongest muscles naturally determining the posture) or are they due to organic brain changes which are the cause and not the result of epilepsy?

Heilig and Steiner (11) found epilepsy present in 41% out of 294 families that contained one or more left-handed members, and not a single epileptic in 294 families who were entirely right-handed, while Bardeleben (12) thinks right-handedness is due entirely to education. According to Focher, Schultze (13), Gauter (14), Gött and Wildbrette (15) found that children of left-handed families are especially disposed to convulsions, while Redlich (16) thinks left-handedness and epilepsy due to mild and unnoticed attacks of encephalitis in early childhood.

Benedikt (17) thought that cranial measurements were an indication of epilepsy while Jellinek (18) took the opposite view.

The brain possesses a relationship in the body that no other organ of the body possesses—namely, that it sends out to, and receives impulses

from, every organ in the body, and that these functions are connected by commissural fibers. It is practically impossible to exclude an organic lesion except by a study of serial sections. Large destructive lesions are less apt to produce epilepsy than small lesions and these may be easily overlooked in an autopsy. Particularly is this so because a large lesion produces destructive changes, and would therefore no longer be classified as epilepsy, and each known organic brain disease with convulsions is at once taken out of this classification. However, Sargent says "If there is a fundamental precipitating cause for all convulsive attacks, any hypothesis which does not take into account the pathogenesis of fits originating in the neighborhood of a gross lesion, must fail to touch that essential point."

There is no doubt that brain tumors often produce convulsions. In Barker's *Monographic Medicine* it is stated that 60% of brain tumor patients have convulsions, while MacRobert and Feinier (20) found generalized epileptic seizures in only 4 out of 165 cases of brain tumor.

McKendree and Feiner (21) in 100 verified cases reported 32 cases of somnolence, and of these, three showed convulsions, one Jacksonian attacks and two petit mal. The three showing convulsions were temporo-occipital, parieto-occipital and fronto-temporal, the Jacksonian case was frontal, and of the petit mal cases one was cerebellar and one temporal.

MacRobert and Feiner state that generalized epileptic seizures occur in 50% of temporosphenoidal lobe tu-

mors. Ferrier and Mills found them present in 13 out of 27 cases, Kennedy in 4 out of 9 cases.

In the series of 165 cases of brain tumor reported by MacRobert and Feinier (22) generalized epileptic seizures occurred almost exclusively in temporosphenoidal tumors. In the five cases of temporosphenoidal lobe tumors three showed major epileptic seizures, and two showed generalized convulsions without loss of consciousness. The only other tumor causing major epilepsy was one in the post parietal area.

In the case reported by Verger, Pautat and duFayet de la Tour (23) a glioma of the right frontal lobe for 9 years previously had seemed to be a typical case of epilepsy (age 35 years).

Is there any particular part of the brain in which a tumor is more apt to produce convulsions than in any other part of the brain? Neurologists are practically agreed upon the fact that the clonic convulsions are due to the cerebral cortex although they are not completely in accord as to whether this represents a cortical stimulation or a cessation of the activity of the cortex, removing its control over the subcortical centers, which according to some writers produce the convulsions. The results of cortical stimulation by the faradic current are well known and need not be reviewed here, but it is interesting to note that Beever (24) found that a mild current caused a contraction on the opposite side of the body in the muscles represented in the stimulated cortical area, while a stronger current produced a contraction first on the

opposite side and then on the same side, while a still stronger current produced a simultaneous convulsion on both sides—and that no epilepsy was obtained on the same side as the cortex stimulated, when the opposite cortex was removed. This is very suggestive of the fact that there may not be any real difference in a Jacksonian attack and a general attack, and that it is more a matter of degree than kind. In other words, the strength of the stimulus, or the irritability of the brain is probably the determining factor in the production of Jacksonian or general convulsions.

An area of the brain is sometimes abnormally sensitive without any apparent cause. Stimulation of an epileptogenous zone in Jacksonian epilepsy, even when no lesion is found, will produce a convulsion with a mild current, while a stronger current fails elsewhere.

In the vast majority of cases of epilepsy there is no history of a tonic spasm. Pollock (25) says the medulla and pons participate in the convulsion in all cases of epilepsy, whether the site of the discharge is there or not. "It would seem that epileptogenous qualities are possessed by the ganglion cells both of the brain and brain stem, that convulsive movements may be evoked by proper stimulation of such cells at any level, and that the first symptom produced depends upon the level so stimulated." Ziehen (26) attributes the clonic convulsions to the cortex and the tonic spasm to the subcortical centers. The evidence seems mainly in favor of this view. We believe now, however, that the cortical control allows the

subcortical centers to produce the tonic contractions, and that the gradual restoration of the cortical function produces the clonic spasm.

As far as the cerebellum is concerned there is very little evidence that it ever produces clonic spasms, the extremely rare cases reported probably being due to great increase in intracranial pressure.

Kennedy thought that "generalized epileptic seizures result more often from neoplasms in the temporoparietal lobes than from tumor formations in any other cerebral area." "On this account MacRobert and Fenner advanced the theory that the topographical relation of the sylvian artery to these lobes renders the former susceptible to abrupt compression from the transient edemas surrounding the growth" which they believe render the cortical elements unstable, but Kennedy interprets it as a cutting out of the cortex leaving the lower levels released from cortical control.

In 100 cases of verified brain tumors studied by Drs Chas E Dowman and Wm A Smith, general convulsions occurred in 19%, and Jacksonian attacks in 14%, tonic in 2% and uncinata in 2%. Of the generalized attacks, the tumor was located in the frontal or precentral region more often than any other one region (4 cases each) and temporal lobe (3 cases), while those with general and Jacksonian attacks showed convulsive movements in frontal 4, precentral 10, temporal 5, or a total of 19 in these regions. In the cases without convulsion there were 6 frontal, 8 precentral, and 6 temporal or

a total of 20 cases. From these figures there seems to be about an even chance of convulsions or no convulsions from tumor in these three regions. As to increase in intracranial pressure as judged by the presence of choked disc the cases with convulsions showed choked disc in 31 cases, none in 8, while the cases without convulsions showed choked disc in 39, none in 22.

MacRobert and Feinier stated that epileptic convulsions are not due to increased intracranial pressure caused by the tumor, for in 45 cases (of cerebellar tumor) of their own and in 40 cases of Stewart and Holmes generalized convulsions did not occur. They state that internal hydrocephalus (dilated lateral ventricles) was found in one third of the autopsies on epileptics at the Craig Colony, which may also produce a compression of the sylvian artery.

Frequent references are found in the literature to ammon's horn as being the special seat of epileptic attacks.

Kogerer (27) thought that the sclerosis in the cornu ammonis had a relationship especially to epilepsy and that the cornu ammonis reacted more sensitively to convulsive stimuli than other parts of the brain.

Kogerer (28) found the ganglion cells in ammon's horn were filled with a large number of corpuscles which showed fat stain in scarlet and in Marchi's stain. The blood vessels were dilated and gorged with blood and in spots changed to hyaline masses. There were lumps of degenerative material within many of them and upon

the outer wall. The patient died in status epilepticus.

Weimann (29) finds degenerative and sclerotic changes in the cornu ammonis in many different conditions and does not regard the changes as throwing any special light on convulsions.

Hajos (30) reported 4 cases of epilepsy in which there was cellular degeneration and sclerotic changes.

Hermann (31) found symmetrical apoplexy in ammon's horn in one case which would more probably be an effect than cause.

Do generalized epileptic attacks occur in cerebellar tumors? Collier (32) found that very rarely generalized epileptic seizures may occur in cerebellar tumors but only late in the course of the disease.

Stewart & Holmes (33) in a series of 40 cases of cerebellar tumors did not have a case of generalized convulsion.

MacRobert & Feinier (34) in 45 posterior fossa tumors found only 9 cases that had anything like fits, 4 of which showed tonic spasm, 2 cranial nerve attacks due to irritation and 2 facial nerve tics, none generalized convulsions.

Turning now to trauma as a cause of epilepsy, in 19.5% of my cases there was a history of injury to the head, not including fractures, gun shot wounds, etc., but the injury was sufficient to produce loss of consciousness.

Trauma to other parts of the body occurred in 8.5%.

4.5% of Sargent's reviewed cases of craniocerebral wounds in the late war

developed epilepsy (800 cases out of 18,000 studied)

Out of 138 cases of war wounds of the skull operated on by Gamberini (35) epilepsy developed in 44 of those traced, in 10 cases only after .2 or 3 years

Robertson (36) quotes Voss (37) who found that 56% out of 116 cases of trauma of the brain that had seizures, the lesion was in the parietal region, the others occurred in various parts of the brain

Della Torre (38) also believed that the parietal region is the most often involved in seizures of epileptiform character. He believed that epilepsy developed in 9% of those who received wounds of the head in the world war

It is generally conceded that essential epilepsy is not only characterized by convulsions but that there is a constitutional inferiority of the brain, something in its make up that predisposes some individuals to convulsions, an abnormal personality, a convulsive aptitude, or lessened resistance to influences from within and from without, which in a normal individual would not give rise to a convulsive form of reaction. Some writers have taken the attitude that the convulsions lead to mental deterioration, which is no doubt true in many cases, while others think that the mental deterioration permits the convulsions, which also seems true in many cases

Block in a study of 200 cases of epilepsy found 11.5% occurred in children who were backward or mentally defective. About 25% of mentally defective children have epilepsy. Geitlin (39) suggests that the rea-

son why epilepsy does not occur in all idiots and imbeciles may be because the subcortical centers are too pathologic to respond. "Forty five per cent of all infantile cerebral palsies develop epilepsy. This occurs in about 50% of the cases of hemiplegia, 30% of all forms of diplegia, and 36% of paraplegias"—Elsner (40). The mildest cases of cerebral hemorrhage are often followed by the most severe epilepsy. In severe hemorrhage the degree of paralysis is sufficient to prevent the convulsions taking place, as in the disappearance of convulsions on one side in epileptics following a hemorrhage into the internal capsule.

Thom (41) studied 109 children who had developed convulsions under 4 years of age—one group (47 cases) show no brain damage, and are considered normal and have had no convulsions for 7½ years. Sixty two cases belong to the brain damage group, and 24 of the 42 cases having convulsions associated with gastro-intestinal upset, in later life showed brain damage. Epileptic convulsions are much less common after apoplexy in adults than after apoplexy in children.

While not wishing to minimize the importance of extracranial causes of epilepsy there is quite sufficient evidence that we cannot ignore the fact that there are many intracranial causes. Just what the chief factor is in provoking the attacks, either in an otherwise supposedly normal brain, or in an abnormal brain, is open to discussion. There is considerable evidence that cerebral anemia plays an important rôle.

It is well known that pallor is usually the first symptom of the onset of an epileptic seizure. The rigidity of the chest then produces congestion and cyanosis. The retinal arteries have been found narrowed on ophthalmoscopic examination during the paroxysmal attacks of impairment of vision which occur in some cases of epilepsy—Russell (42)

Savill (43) says hemorrhage, thrombosis and embolism are accompanied by epileptic seizures in about 33% of cases. In such cases the damage must have been considerable and of such a degree always as to be followed by some hemiplegia.

Richter (44) says "The pathogenesis of these conditions was found in a local ischemia as a result of a vascular spasm and insufficient blood supply" (quotes Pol). Richter's conclusion is that in hemicrania an angiospasm occurs in the region of the blood supply of the vertebral system and the inferior cervical sympathetic ganglion. In epilepsy the motor cortex is involved. The carotid artery and superior cervical ganglion are affected.

Pol also concludes that migraine and epilepsy represent two types of vascular crises affecting different vessels and different areas.

Kennedy (45) observed the parietal cortex of the brain during a general epileptic fit while under local anaesthesia. The initial sign of the seizure was a sudden whitening of the cortex followed by a tremendous venous engorgement with protrusion of the brain beyond the level of the bone defect, and coincident with this was

the tonic stage of the attack and the period of general clonic convulsion.

Pätzl and Schlaffer (46) observed local edema of the surface of the brain coincident with a seizure during the operation for Jacksonian epilepsy. They produced similar changes in a dog by faradic stimulation of the brain cortex. The writer observed a case with complete right hemiplegia, both motor and sensory, and on observing the brain exposed under a local anaesthetic there was a complete ischemia in the area of distribution of the ascending parietal branch of the middle cerebral artery but at no time were there any convulsions, nor was there edema present. It is probable that the total loss of sensation was the factor that prevented convulsion taking place, as well as causing a flaccid instead of a spastic type of hemiplegia.

Kennedy (47) reports the case of a girl with giant urticaria and generalized epileptic convulsions, clonic, but no tonic phase, due to cortical irritation, "rather than by a sudden cutting out of the cortex and the transient production of a decerebrate rigidity, such as characterizes the first phase of an ordinary epileptic seizure." It has long been known that pressure on the carotid vessels or ligature will cause convulsions, and they may be produced by the hypodermic injection of vasoconstrictors, as 1% adrenalin chloride (10 c.c. to 15 c.c.) or cocaine (0.03 grm. to 0.05 grms.) in epileptics.

In Stokes Adams syndrome, as a result of cerebral anemia (the auricle continues to beat, but the ventricle either beats very slowly, 5 or 6 to



the minute, or not at all), a convulsion occurs

Pike (48), Stewart, Guthrie, Burns and Pike produced loss of consciousness and asphyxia in cats by ligating the internal carotid and vertebral arteries. After ten minutes the ligatures were loosened, and this was immediately followed by a series of convulsions, which could be provoked by external stimuli. "In a few cases of human epilepsy it has been noted that the tonic phase of the fit occurred coincidentally with the arrest of the circulation, while the clonic phase was ushered in with the resumption of the radial pulse, and the heart beat"

In the cases observed by the writer the muscular contractions were not synchronous with the heart beats, the latter being many times as rapid, although the radial pulse could not be felt at all during the attack. There is said to be a cessation of the heart during the tonic stage, while the clonic stage comes on when the circulation returns in spurts to the brain.

Cuneo (see Osnato (49)) says proteoses or epinephrin may cause convulsions when painted on the cerebral cortex or lactic acid when injected intravenously. Cuneo found proteoses in the blood of epileptics and could produce convulsions by injecting proteoses into the blood stream, and he attributes the convulsions to the splitting up of the nucleohistone in the nerve cells into nucleic acid and proteoses, the latter remain free and exhibit their convulsive action, which Osnato thinks is due to a constriction of the cerebral vessels and through

this means causes the loss of consciousness.

Osnato says the factor of importance in epilepsy is the acidosis, regardless whether this depends on a viciously functioning carbohydrate metabolism which causes a general toxicosis, or upon the local production of the toxic substance from disintegrating structures, secondary to vascular disturbances. The vasoconstriction might be caused by several toxic substances; proteose in so-called idiopathic epilepsy, epinephrin or some other substance in the so-called psychogenic (emotional factor) cases.

Elsberg and Stookey (50) found that animals in whom normal saline solution is allowed to circulate through the vessels of the brain, during the period of cerebral anemia, do not have any convulsions after the intracranial circulation is reestablished.

Are the cases in which the attacks can be produced by peripheral stimulation due to organic brain disease?

Block reported a case in a negro boy with left hemiplegia who had attacks whenever he stumped his left toes or whenever his left foot was struck. Here was an organic brain injury in which the attacks could be brought on by a peripheral impulse and it would be interesting to know if all the cases in which the attacks are precipitated by an afferent impulse have not also an organic change in the corresponding brain area.

Pontano (51) in reporting a case of glioma of the sensorimotor zone also held the view that reflex epilepsy can be provoked only from zones in the skin corresponding to the affected parts of the cerebral cortex.

Herman (52) reports a case in which the seizures could be provoked by manipulation of the limb in which the aura was present. It is to be supposed that the aura was of cerebral origin.

#### SUMMARY

1 Organic brain disease often shows no other evidence than convulsions, and epilepsy is the only warrantable diagnosis, until other signs or symptoms appear, or until an autopsy reveals organic disease. Especially is this true when the lesion is in a latent area of the brain. The lesion is usually a small one.

2 There is no one area of the brain that is responsible for all epileptic fits, although the cerebellum may be ruled out as far as epilepsy is concerned. Tonic fits may occur from cerebellar lesions, and in tumors, exerting great pressure, convulsions may occur late in the disease, but the evidence of organic cerebellar disease would exclude a diagnosis of epilepsy.

3 Tonic fits are due to withdrawal of cortical control, and the activity of the subcortical centers produce the tonic phase of the convulsion, the chief control being in the red nucleus.

4 Cerebral anemia (angiospasm, or pressure upon the blood vessels) plays an important rôle in the production of the attacks.

5 In cases in which convulsions are provoked by peripheral stimulation there is reason to believe that they are due to the reception of an abnormal brain, and would not occur if the brain were normal.

6 Both a sensory and a motor component are probably necessary for the production of epileptic attacks, as is shown by the cessation of epilepsy after the development of tabes dorsalis, shutting off the proprioceptive impulses, and by the absence of convulsions in destruction of the function of the cortical sensory area, although tonic spasms may still occur from impulses arriving in the subcortical centers from below.

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# Agranulocytic Angina with Thrombopenic Purpura

By WM ALLAN, M D, *Charlotte, North Carolina*

SINCE Schultz' (1) report in 1922 of the condition since known as agranulocytic angina, the recognition of this disastrous malady is becoming steadily more frequent both in Germany and in this country. A year ago Kastlin (2) reviewed 43 cases and since his report, cases have been reported by Finnigan (3), Hart (4), Carnot (5), two by Linthicum (6), Ashworth and Maphis (7), Gundrum (8), Whitehead (9), and Sachs (10), making a total of 52 cases.

The onset is abrupt with sore throat, high fever, chilliness, general aching, prostration, headache, and sometimes vomiting. Herpes may appear and half the cases show some jaundice. In all, the oral cavity becomes ulcerated and bleeds, either tongue, gums, tonsils, or pillars, and in half this ulceration is membranous, suggesting diphtheria. Similar ulcerative lesions are found in the vagina, on the cervix and around the anus. The neighboring lymph glands are usually not enlarged. Either liver or spleen, or both, may be enlarged. Kastlin reports that eight of the 43 cases he reviewed had subcutaneous ecchymoses, and visceral ecchymoses were seen in 12 of the 34 that came

to autopsy. More than 90% die within a week or two.

This syndrome can be recognized only by examination of the blood. Kastlin reports a decrease in the leucocytes in 41 out of 43 cases, the average count being 1,200 white cells, the lowest 100. The polynuclears vary from 0 to 6% and the lymphocytes from 60 to 100%. The number of red cells was normal in 25 out of 33 cases, and in eight there was secondary anemia. In 20 out of 27 cases the platelet count was normal, and this finding seemed to bear no relation to the occurrence of purpura. In Gundrum's case the icterus index was 16. The coagulation time was found to be normal in Kastlin's first case and in Ashworth and Maphis' case. The bleeding time in Kastlin's first case in which purpura was present, was 25 minutes. With very few exceptions, blood cultures have been unproductive.

In Whitehead's case the platelets numbered 165,000, there was no hemorrhagic tendency, and the reticulocytes varied from 0 to 1%.

Treatment has been entirely unsuccessful. Blood transfusion seemed to be beneficial in Finnegan's case, but Gundrum, Cannon (11), Pfab (12),

and others have found this measure useless

At autopsy the ulcerated areas show no leucocytic reaction and in the bone marrow leucocytes, myelocytes and myeloblasts are absent the red cell germinal centers and megakaryocytes are uninjured

Case report *May 24, 1928* A white farmer, age 30, was referred to me by Dr C I Allen, of Wadesboro, N C The patient complained of weakness and sore throat, was pale and had purpura and high fever His family and past history were unimportant He used neither tobacco nor alcohol and denied venereal disease The present condition had started eighteen days before when he developed sore throat with fever and what seemed to be "a rising" in both tonsils The left tonsil was lanced and continued to bleed for a week On the third day of his illness he developed purpura over both shins He has had rather high fever all the time Except for some discomfort on swallowing with occasional regurgitation of coffee through the nose there has been no pain He has had no joint symptoms and no abdominal symptoms

Physical examination showed the skin very pale with a slightly lemon tint but sclerae clear Scattered thickly over both shins and sparsely over arms and chest were small discreet purpuric spots There were wide spread retinal hemorrhages The throat showed both tonsils very large and ragged The appearance of the mucous membrane over the pillars and posterior pharynx was a dull glazed brick red The tissues behind the left tonsil were swollen so as to shove this

tonsil over until it touched the uvula The right side of the throat was only slightly swollen The gums at the margin of the teeth were covered with a dirty grey deposit There was no enlargement of the superficial glands anywhere Neither spleen nor liver was palpable, and the physical examination was otherwise negative

Dr J P Matheson found the left side of the throat very firm and hard, but incised the indurated tissue behind the left tonsil freely This continued to bleed for several hours until at the suggestion of Dr Charles Allen a hemostatic serum (Lapenta) was injected directly into the tissue

Examination of the blood showed hemoglobin 30%, red count 1,330,000, color index 1.1, red cells were normal in size, shape and color reaction, and there were no blasts Leucocytes numbered only 1,200 with polynuclears 6%, lymphocytes 94%, no blood platelets were seen in the smear The clotting time was six minutes, the bleeding time 75 minutes, with a platelet count of 15,000

At 1 A M, May 25, the patient was given a citrate transfusion of 600 cc of blood, followed by 300 cc of saline by Dr Barret This was followed by a moderately severe reaction Late that afternoon the hemoglobin was 45%, red count 1,960,000, red cells normal in size, shape and staining reaction, no blasts, an occasional platelet was seen in the smear Leucocytes numbered 1,400 with 4% polynuclears, and 96% lymphocytes

On May 26, the patient was given a second citrate transfusion of 500 cc of blood

May 27, a large ulcer has appeared on the right side of the tongue. The patient's color and pulse are better and the purpura and retinal hemorrhages have faded very considerably. There has been no bleeding since the first transfusion and the amount of blood lost from oozing following the throat incision was negligible. In spite of such objective signs of improvement, the patient became more drowsy with the type of breathing that suggests acidosis and died at midday.

The other conditions that show a decrease in total leucocyte count with especially diminished polynuclears are toxic poisoning, such as arsenic and X-ray, fulminating purpura, aplastic anemia, acute overwhelming sepsis and possibly leukemia when these cases show a low blood count.

In the present case there has been no history of exposure to toxic poisons

and according to Pratt (13) fulminating purpura is confined to infants. In a great majority of cases, as there is no anemia, there is no necessity for differentiating this syndrome from aplastic anemia, but should angina and high fever be added to aplastic anemia the differentiation would be impossible.

Many authors think this picture is simply one type of an overwhelming sepsis without reaction, and if they are correct, no differentiation from sepsis will be needed. In the present instance there is nothing to suggest either acute or aleukemic leukemia.

In the case presented here the clinical course, objective signs and blood findings were all typical of agranulocytic angina, and in addition, there was a much more severe thrombopenic purpura than had previously been reported.

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# Undulant Fever in Connecticut with Reports of Three Cases

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UNDULANT fever, known also as Malta fever, Mediterranean fever, and Gibraltar fever, is characterized by continued fever, or fever with short remissions and relapses, neuralgic pains, joint swelling, orchitis, and profuse perspiration

## DISTRIBUTION

Text books state that undulant fever has not been reported north of latitude 45°N or south of 40°S latitude. It is known to have occurred in every part of the island of Malta.

Orr and Huddleson (1) have reported sixteen cases of undulant fever occurring in Michigan from June 1926 to October 1927. Cases of undulant fever due to the *Bacillus abortus* have been reported in New York State by Carpenter (2).

Keefer (3) reported a case of Malta fever occurring in Baltimore, Maryland, in 1922.

Sensenich (4) and Giordano recently reported seven cases of *Brucella abortus* infection occurring in Indiana.

Up to the present time there have been sixteen cases (5) reported in the state of Connecticut. Of these, three have occurred in Meriden, Conn.

## ETIOLOGY

The micrococcus *melitensis* is the causative organism. It is 3 micromillimeters in diameter, is non-motile and is gram negative. It grows very slowly and is difficult to grow in culture. Acid media should be used, and the culture should be carried through for eleven or twelve days. Since it has been recognized that there is a very close relationship between the *Bacillus abortus* and the *Micrococcus melitensis*, the bovine source of infection has added to the seriousness and importance of this disease.

In 1914 Kennedy (6) testing goat's milk for agglutinins specific to the micrococcus *melitensis*, found the control cow's milk gave a positive result. Goat's milk has been the chief offender. It is thought that the larger number of cases have come from infected cattle. This seems to us to be very doubtful. McAlpine and Mickle (7) have reported on their investigations of a very large number of dairy herds in Connecticut. Of this large number 90% were shown to be harboring the *bacillus abortus*. If this is so why are not more people infected with undulant fever? Knowing that cattle can be infected by the porcine



strain, isn't it much more likely that only the cattle harboring the porcine strain, can transmit the disease to man

The incubation period is thought to be about fourteen days, although this is difficult to determine

### IMMUNITY

There is some difference of opinion concerning immunity, but one attack is thought to confer protection from subsequent infection

### SYMPTOMS

The disease begins insidiously. The patient usually feels well in the morning and on toward evening complains of feeling hot and tired. The temperature in the morning is usually under  $100^{\circ}$  and in the evening ranges between  $100^{\circ}$  and  $104^{\circ}$ . This is usually followed by marked perspiration. Constipation is a common symptom. Neuralgic pains are usually complained of by the patient. Later on the usual symptoms of a secondary anemia are seen.

### MORTALITY

The mortality is not high. About one to three percent of cases are fatal. The duration of disease is usually about four or five months, although it may be considerably more or less.

### DIFFERENTIAL DIAGNOSIS

Frequently diagnosis by exclusion is necessary. The diseases most often confused with undulant fever are typhoid, tuberculosis, subacute bacterial endocarditis, and aestivo-autumnal ma-

laria. Blood culture and Widal will usually suffice to separate typhoid. The clinical picture and blood culture will aid in the diagnosis of subacute bacterial endocarditis. Tuberculosis can be ruled out by physical examination, sputum, and X-ray, aestivo-autumnal malaria, by demonstrating the parasite in the blood smears.

### DIAGNOSIS

Diagnosis is accomplished by the history of undulating fever, accompanied by pains in the joints, and by recovering the organism in the blood culture. At times this latter is very difficult. With a clinical picture of undulant fever, and with a positive agglutination of the micrococcus melitensis up to at least 1:200, one is justified in making a diagnosis of undulant fever. This is particularly true when the simulating diseases can be ruled out.

A cutaneous test for the diagnosis of this disease has been suggested by Oliver and Massot (8). It consists of the injection of 1/10 to 1/20 cc of a filtrate of micrococcus melitensis into the skin. In positive cases there is no general reaction, but at the site of injection there is local oedema, redness, and pain appearing between six and twenty-four hours.

### TREATMENT

The treatment is largely symptomatic. In the chronic cases, vaccines made from the micrococcus melitensis and para-melitensis have been advised.

### PROPHYLAXIS

Removal from the diet of all suspicious foods is indicated, particularly

goat's milk and its by-products and also, suspected cow's milk

# CASE REPORTS

*Case 1* P R Age 32 yrs Catholic Clergyman The patient was first seen on December 29th, 1927 The family history was unimportant

## Past History

Fractured right leg ten years ago Three years ago was in hospital with rheumatism which cleared up following extraction of teeth

## Present Illness

Patient complained of sore throat, pain in neck and cough This has been going on for the past four days The temperature was 100°

## Physical Examination

Pupils equal and react to light and accommodation Mucous membrane of nose and throat inflamed Cervical glands slightly enlarged Thyroid normal Heart regular, no murmurs Heart not enlarged Bl Pr - 116-60 Lungs negative Liver and spleen not palpable. No tenderness in abdomen Right leg 3/4" shorter than left. Knee jerks normal Babinski and Koenig negative

The temperature returned to normal on January 2nd/28 and remained so until January 11th/28 On this date it went up to 102° This elevation continued for about four weeks He was admitted to the Meriden Hospital on February 7th/28 The only additional signs on physical examination were râles in the bases of both lungs, and some general weakness During his stay in the hospital, he had two remissions when the temperature came down to 99° and remained so for about three days when it again became elevated He was discharged from the hospital on April 6th/28 His temperature had been normal for one week, and has remained so since then

## Laboratory Findings

Urine—1018 ac cl albumin negative Sugar negative Erythrocytes 4,400,000 Leucocytes 10,000 Polys—65%, Large—12% Small—23% Blood cultures Jan 14th/28, Jan 23rd/28, and Feb 3rd/28 were nega-

tive. These were all taken at the height of fever Agglutination for typhoid and para-typhoid A and B were negative Smears for malarial parasites were negative The blood in dilutions up to 1:300 agglutinated the *alcalignes melitensis* X-rays of chest were negative Repeated examinations of sputum were negative for tubercle bacilli

## Diagnosis

Undulant fever

## COMMENT

It will be seen that this patient had three relapses from December 29th, 1927, until his discharge from the hospital on April 6th, 1928 The *alcalignes melitensis* was agglutinated by the serum in dilution of 1:300

*Case 2* Mr F H Age 44 yrs Married, no children Salesman Territory was through the west and southwest The patient was seen in consultation with Dr J D Eggleston on January 16th/28 The family history and past history were unimportant He had been ill for three weeks The chief complaint was elevation of temperature, usually during the afternoon or early evening The other symptoms were weakness, and occasionally pains in the legs Subsequently a history of inordinate craving for cheese was obtained

## Physical Examination

The pupils react to light and accommodation Conjunctivae pale There is some bridge work in mouth Nose negative No tenderness over sinuses No cervical glandular enlargements Thyroid normal No facial palsies Heart sounds are soft There are no murmurs The heart is not enlarged Bl Pr—128-70 Lungs—rales in the bases of both lungs Arms are a little flabby There are two small petechiae on the left hand in back Abdomen—liver and spleen just palpable at the costal margins Back is negative Legs not edematous Knee jerks normal Babinski and Koenig negative.

## Impression

Subacute Bacterial Endocarditis

*Laboratory Findings*

Urine—1028 ac cl albumin negative  
 Sugar questionable. Erythrocytes, 3,750,000  
 Leucocytes, 10,000 Hb—70% Polys—63%  
 Large mononuclears—14% Small mononuclears—30%, Eos—3% Non-Protein Nitrogen—33 mgs in 100 cc of blood Blood Sugar—166 mgs in 100 cc of blood Blood Wassermann negative Blood culture negative The agglutination for typhoid, and para-typhoid A and B were negative Blood smears for malarial parasites negative The serum agglutinated the *alcalignes melitensis* in dilutions up to 1:300 The radiograms of teeth, sinuses and chest were negative The blood culture was repeated on January 27th/28 This was taken at the height of fever but no growth could be obtained The temperature returned to normal on February 15th/28 and remained so

*Diagnosis*

Undulant fever

## COMMENT

The noticeable facts about this patient were his craving for and his eating of large amounts of cheese The territory in which he traveled would include some of the states which have reported cases of undulant fever

*Case 3* Mrs R T Age 43 yrs Housewife, married, two children No miscarriages

The past history is negative excepting some nervous conditions about six years ago, which quickly cleared up

The patient consulted us on January 20th/28 She complained of pains in lower part of her back and thighs for the past two weeks For one week she has known that she had an elevation of temperature This ranged from about 100° in the morning, to 103° in the late afternoon or evening When questioned closely, she believed from her symptoms that she must have had an elevation of temperature about one month ago, with a subsequent remission

*Physical Examination*

The pupils are equal and react to light and accommodation The nose and throat

are negative There are some suspicious teeth There are no cervical glandular enlargements The thyroid is normal The heart is not enlarged There is a murmur at the apex Systolic in time The blood pressure is 114-70 The liver and spleen are not palpable There are no masses felt in the abdomen Rectal and vaginal examinations are negative The knee jerks are normal The Babinski and Koenig are negative

*Laboratory Findings.*

Urine—1020 ac turbid, albumin negative, sugar negative Microscopical—Occasional pus cell No clumping Erythrocytes, 4,800,000 Leucocytes—8,800 Polys—65%, Large mononuclears—11%, Small mononuclears—23%, Eosinophiles—1% Blood Wassermann negative Non-Protein Nitrogen—25 mgs in 100 cc of blood Blood Sugar—110 mgs in 100 cc of blood Blood culture negative Agglutination for typhoid and paratyphoid A and B were negative Blood smears for malarial parasites negative The blood agglutinated the *alcalignes melitensis* in dilutions up to 1:300 X-ray of teeth showed some suspicious teeth

*Diagnosis*

Undulant fever

Blood cultures were taken on January 20th/28 and February 1st/28 at the height of fever, but no growths were obtained The patient had two remissions between January 20th/28 and March 10th/28 with relapses Since March 27th/28 the temperature has remained normal

## COMMENT

It would appear that undulant fever due either to the *bacillus abortus* or to the *micrococcus melitensis*, is more widespread than was formerly thought With the number of cases which are being recognized in Connecticut, it is probable that this disease occurs in areas not heretofore considered

The question of the habitat of the causative agents we are sure, will demand further investigation If the

bacillus abortus is being harbored in the udders of cattle, why are not more people infected? Are the porcine and equine types more frequently found than the bovine? These are questions which must be answered

Signs and symptoms of bronchitis as characterized by cough and râles in the bases of both lungs, were symptoms common to all three patients reported in Meriden

#### CONCLUSIONS

1 Undulant fever is probably more common in Connecticut than was heretofore thought Three cases are reported in Meriden, Conn

2 In all three cases the serum agglutinated *Alcaligines melitensis* in dilutions up to 1:300

3 Further investigation as to the habitat of the causative organisms and the avenues of infection is warranted

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# On the Treatment of Acid Mouth

By J E RUSH, M D., and W W ZWICK, M D., *Department of Hygiene and Public Health, University of Kentucky, Lexington, Kentucky*

THERE are a great many symptoms which become exceedingly distressing to a patient, and though these may never cause death, their alleviation becomes exceedingly important in the eyes of the patient because of the great annoyance occasioned

Among these, perhaps, may be mentioned that rather frequent condition known as acid mouth "While one swallow does not make a summer," the following case is reported with the realization that to generalize from a single case is not only dangerous but actually unscientific. The result of this case is thought to be of interest because other physicians with a more extensive practice may be able to reach definite conclusions by further experiment along the same lines

When no definite pathological basis can be found for a condition in which the saliva is acid to the extent that considerable erosion of the teeth takes place, and when it has been established (by exclusion) that such erosion is probably due to the bacterial flora present, and the resulting fermentation in the mouth, it would seem that the local measures described below might be instituted with the idea that they would be as successful in some other case

On April 14, 1926, M C., a female patient, age 43 (circa) presented herself to the University of Kentucky Dispensary. She had been under treatment for the condition known as acid mouth, by physicians, for some years previously, and though originally she had a beautiful, strong, sturdy set of teeth, the erosions near the gum margins were in some cases a tenth of a centimeter or more in depth. The teeth of this patient presented the most marked erosions I have ever seen. She was put on the usual treatment to attempt alkalization, namely, sodium bicarbonate by mouth and an alkaline mouth wash. As this treatment had been instituted on previous occasions by other physicians and the patient received no beneficial results therefrom, it was only a few days until she was back again feeling that she was making no progress under this treatment. At this time, we were called in consultation, and while we had never been interested particularly in the treatment of such conditions, the results on a priori grounds seemed to indicate that the treatment then being instituted was contraindicated, if this condition was due to a localized condition of the mouth, in virtue of which a bacterial flora capable of acid production

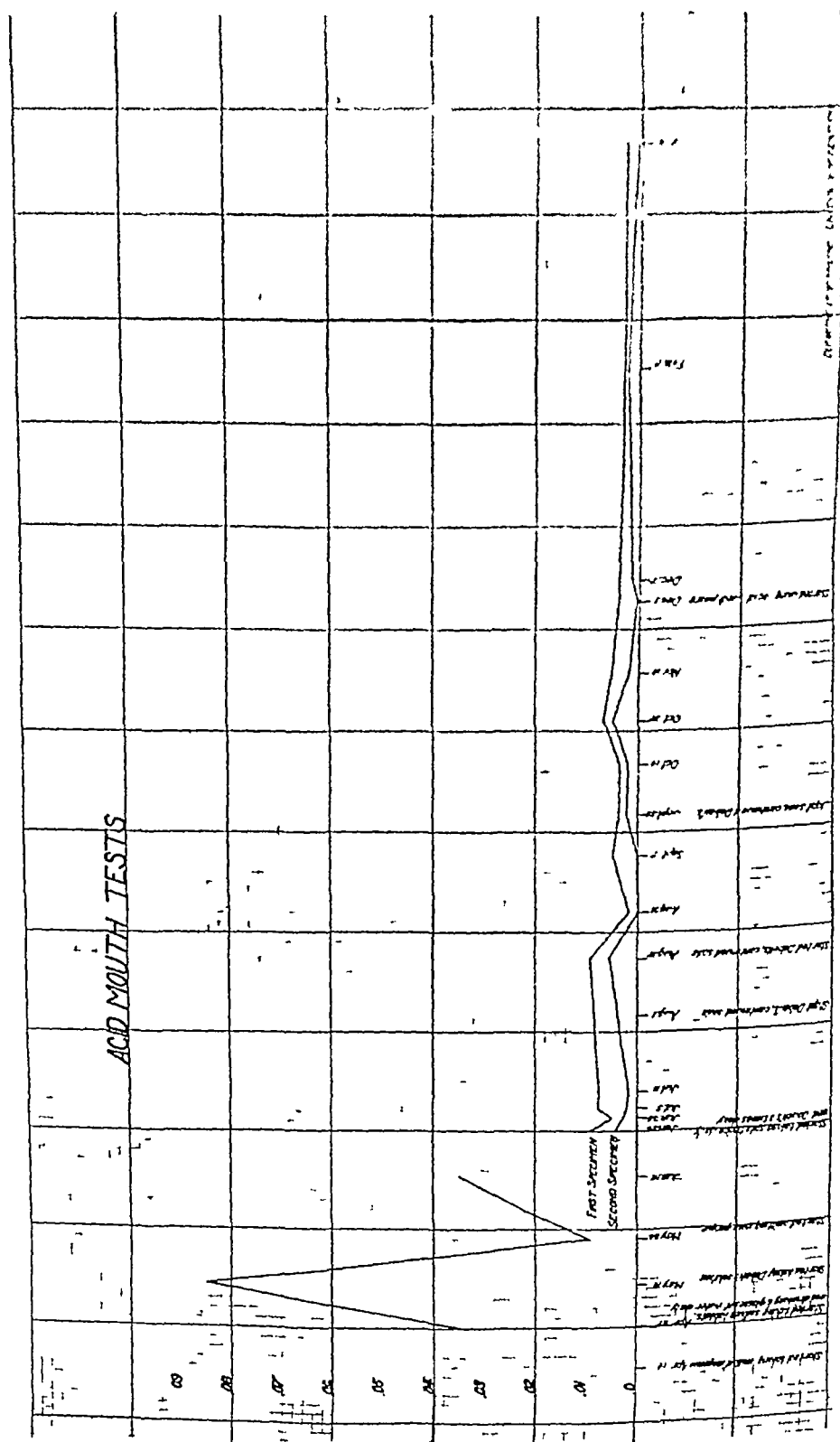
had entrenched itself Obviously, the thing to do was not to remove the acid by alkalization, allowing the reaction to proceed farther, as any chemical reaction does upon the removal of the end products made, according to the law of mass action resulting when applied to the case in hand in further erosion of the teeth

A parallel condition and procedure was cited to this case of the application of lime to a soil for the neutralization of acidity On these theoretical grounds, it was decided that to occasion a reaction in the other direction, which meant that the treatment to be instituted should be of an acid character Particularly would it be advisable if an acid could be used which, also, possessed some bactericidal properties In consequence of this theoretical reasoning it was decided to keep the patient, for a time, on the sodium bicarbonate by mouth, and substitute for the alkaline mouth wash, Dobell's solution Thus the patient used three times a day following meals Samples of sputum were titrated by the use of N/100

sodium carbonate and phenolphthalein (for these titrations we are indebted to Dr J H Martin, Chemist, at the Public Service Laboratories, of the Kentucky Agricultural Experiment Station, and Mr D S Ross, of this Department)

The following chart with comments is self-explanatory, and shows beyond peradventure that in this single case the results in reducing the acidity of the saliva were unquestionably due to Dobell's solution

The acidity of this patient's saliva is now (November, 1927) practically the same as it was in April of this year It is apparent from the appended graph that soda and an alkaline mouth wash actually increased the acidity, while the use of Dobell's solution decreased it Theoretically, at least, this should hold the erosion in check, and the patient reports as her opinion, that the erosion has not advanced for over one and a half years since she has been under this treatment, while before this treatment was instituted the erosion was progressing rapidly



# The Constitutional Entity of Exophthalmic Goiter and So-called Toxic Adenoma\*

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\*Address given before the Joint Meeting of the American College of Physicians and the St Louis Medical Society, February 19, 1924, St Louis, Missouri. Although this address was given nearly five years ago the editor has failed to publish it, giving precedence to the rapidly increasing material submitted to the *Annals*. Although published references to this article occur in the literature it is now printed in full for the first time, because of the numerous requests that have been constantly made for its publication. It has seemed wise to accede to these requests by publishing the paper as originally given, since during the last two years the conception of a Graves' disease constitution has found an increasing number of supporters in Europe. A later publication bringing the writer's material and views up to the present time will be published elsewhere.

THERE is perhaps no more interesting chapter in Internal Medicine today than that dealing with disease of the thyroid, in so far as etiology, symptomatology and pathology are concerned. This is particularly true of that large and apparently constantly enlarging clinical syndrome referable to the thyroid embraced under the general conception of *hyperthyroidism*, and variously designated as toxic goiter, toxic thyroid, toxic adenoma, etc., as more or less distin-

guished from typical Graves' (Basedow's) disease or true exophthalmic goiter. From the pathological standpoint the attempt to correlate these clinical groups with the pathologic histology of the thyroid has become an especially fascinating field of study. This study is at present being aided greatly by the flood of resected thyroids pouring into the pathological laboratories, and from the abundance of this material some new facts of importance should come to aid in the clarification of the divergent views on thyroid pathology.

Since the original triad of goiter, tachycardia and exophthalmos was recognized somewhat vaguely by Parry in 1825, much more accurately described by Robert Graves in 1835, and finally given a definite nosological status by von Basedow in 1840, the clinical syndrome, call it, as you will, "Parry's," "Graves'" or "Basedow's" disease, has had added to it one symptom after another until, at the present time, it has become practically impossible to make a positive differentiation clinically between what writers would regard as *true exophthalmic goiter* and what others will call by some other name, as *toxic*



adenoma, toxic goiter, etc. Symptoms referable to nearly every organ or tissue in the body have been brought into the complex; in addition to the classical syndrome, the clinical picture includes more or less constant symptoms referable to the general metabolism, the cardiovascular system, the sympathetic and central nervous system, the endocrinal system, sense-organs, blood muscles, bones, joints, gastro-intestinal tract and liver, genito-urinary system, respiratory system, lymphatic glands and even the skin. In any textbook article on exophthalmic goiter, all of these various symptoms are now regularly incorporated and catalogued as diagnostic factors of primary or secondary importance. The present day conception of Graves' disease is that of an extremely variable and broad syndrome. If we consider this clinical syndrome analytically we see that there is presented the clinical picture of a well-defined type of human individual—a distinct *pathological constitution*. This fact has not hitherto been recognized by American writers on goiter, but in Europe, both in Germany and in Italy, various writers are beginning to speak of the *hyperthyroid constitution*, (or *Graves' constitution*, as I have preferred to call it, in the absence of any positive proof that *thyroid hypersecretion* is its underlying etiological factor.)

The *Graves' constitution* individual presents a youthful build with a slender, delicate and soft skeleton, slender waist, an exaggerated lumbar lordosis, increased articular mobility, long slender fingers and toes with pointed terminal phalanges, abundant hair, and

well developed teeth and nails. The muscles are long and thin, there is underweight rather than overweight. Morphologically, this individual type presents the elements of an ideal beauty adored by so many artists. The face is that of a bright-eyed, snappy, vivacious, quick-reactioned, ingenuous, often very attractive, youthful or childlike appearance; often there is an anxious, unsteady, scornful or angry hauteur in the facial expression. Muscle tremor is practically always present, but may be temporarily absent. Muscle weakness is a common symptom. The skin is usually warm and moist, fine, delicate and translucent, often there is a tendency to excessive pigmentation when exposed unduly to light or local irritation. Vitiligo is not rare. Hyperidrosis is common, and also dermatographia. The throat is usually rounded and full, the cervical lymph nodes are always enlarged. The thyroid is usually enlarged, though not always, all stages may exist between that of no perceptible swelling up to a well-marked diffuse, soft and vascular goiter. Likewise, in the case of the eyes, all degrees exist between the vivacious widely-opened eyelids and prominent eyes to definite exophthalmos. The respiration is usually rapid and superficial. There are vascular pulsations in the neck. The pulse is rapid, quick, full and shows more or less irregularity, the tension is usually slightly increased, and there is marked cardiac excitability with tendency to tachycardia, and vasomotor instability, with hot flashes, flushing, sweating and circumscribed edemas. There is a marked instability of the central nervous system, in

the form of increased sensibilities and emotional response, quickness of perception and reaction, constant unrest and haste, uneasiness, anxiety, breathlessness, insomnia, excited dreams, rapid flow of thoughts, even to hysteria, psychoses, hallucinations, mania and melancholia. Usually, however, the mental powers are well developed and remain well preserved. In the majority of cases the marked irritability of the sympathetic system is a predominant characteristic. The basal metabolism shows invariably a definite increase, the appetite is abnormal, but in spite of over-eating the individual remains thin. Peristalsis is usually increased, even up to attacks of diarrhea, and the amount of stools is usually large. Dilatation of the stomach is frequent. There is a lowered protein assimilation, with an increased combustion of fats, and a lowered tolerance for carbohydrates, as shown by a tendency to hyperglycemia. The so-called "bilious attack" is of common occurrence. There are frequently attacks of polyuria, the chlorides are diminished, while the excretion of calcium and phosphorus is increased. Food idiosyncrasies are common, allergic states are exaggerated, and asthenia is a common symptom. Hyperthermia is a frequent symptom, especially of a psychical origin. The blood shows usually a mild anemia or some degree of chlorosis, the absolute and relative proportion of lymphocytes and large mononuclears is increased. During asthmatic attacks the eosinophiles are increased. Psychical sexual excitability exceeding the physical is not an uncommon characteristic of the type. Impotency is frequent in male patients, menstrual disturb-

ances in the female. Fertility is apparently diminished. In spite of the youthful appearance of the Graves' individual and the increase in energy output the period of reproductive ability appears to be greatly shortened. Spermatogenesis usually ceases in the severe forms. It has also often been noted that sexual experiences frequently bring a latent exophthalmic goiter above the clinical horizon in an especially severe form, not infrequently rapidly fatal. In addition to these most striking characters displayed by the individual possessing the Graves' constitution, there are numerous other minor clinical symptoms that are probably chiefly secondary and acquired from the environment, rather than representing essential intrinsic characters of the constitution. The Graves' constitution individual shows little tolerance for thyroid preparations, iodine and adrenalin. Summing up the most striking and characteristic features of this constitution we find them expressed in *juvenile morphology* and *rapid functional reaction*.

It is quite obvious that these constitutional features just enumerated will appear in varying degrees of intensity and in varying combinations also showing variations in intensity. A great variety of so-called clinical forms of hyperthyroidism described under various terms has unfortunately arisen as the result of the failure of clinicians to recognize the essential foundation entity of these varying clinical pictures. The present clinical conception of "hyperthyroidism" has come to include such an extraordinary range of symptoms that clinicians have found it necessary to divide and subdivide it into a number of type-forms

between which, however, there is no hard and fast demarcation. We, therefore, find in the literature on thyroid diseases the use of such terms as "primary," "secondary," "true" and "classic" Graves' disease, thyreosis, hyperthyreosis, dysthyreosis, hyperthyroidism, dysthyroidism, toxic goiter, toxic non-hyperplastic goiter, toxic thyroid, toxic adenoma, hyperfunctioning adenoma, thyreotoxicosis, struma with Basedow's symptoms, adenoma with Basedow's, formes frustes, incomplete Graves' disease, Basedow's or Graves' constitution, Basedowoid conditions, and in the German literature we find such terms as the basedowification of a goiter or adenoma. While some of these terms are synonymic, they, nevertheless, cover a number of more or less well-defined clinical types. That is, not all of the many symptoms listed above by any means, or even any one of these, is considered absolutely essential for a working clinical diagnosis of one of the type-forms of thyroid disturbances already mentioned. The classical triad, as a whole or in its individual factors, is no longer necessary for such diagnoses, and the clinical diagnosis of hyperthyroidism, toxic goiter and toxic goiter and toxic adenoma is being made frequently today upon the presence of only one or two symptoms that *may* belong to the constitutional picture depicted above, but which may also be dependent upon many other things and not necessarily associated with the thyroid. The most over-worked of these supposed thyroid symptoms are "nervousness and weakness," next to these "cardiac excitability," and next to these "increased metabolic rate." Many normal thy-

roids and simple goiters and adenomas are being diagnosed at the present time as hyperfunctioning or toxic, and are ligolized and operated upon, only to find that histologic examination cannot confirm the clinical diagnosis.

This failure of the pathologist to uphold the clinician has been greatly increased by the numerous cases of iodism occurring, and increasing in number, at the present time. The use of iodine in the prevention of goiter in children has been widely advertised, and there are hundreds, perhaps thousands, of individuals in the goiter regions today who are systematically taking "goiter cures" containing iodine. Sooner or later symptoms appear, principally "palpitation, excitable pulse and nervousness," and resection is ultimately performed, and the pathologist finds nothing but a thin, watery colloid and follicular atrophy present, on which findings he can do nothing more than return a diagnosis of "hyperiodism." In the individual with adenomas an incorrect clinical diagnosis of toxic adenoma is naturally even more frequently made.

Aside from the complicating factor of the overuse and abuse of iodine medication, the wide range of clinical conceptions may indicate a number of things. Differences in etiology, in degree of action of a given cause, or of individual reaction to the latter, constitutional anomalies or predispositions, secondary causal factors, different stages of the affection, variations in the pathological conditions associated with the clinical complex, or simply differences in the diagnostic criteria employed. Probably the last two factors named have served to widen the conception of Graves' disease

more than anything else. The wide range of pathological findings in the resected thyroids from patients regarded clinically as suffering from hyper- or dysfunction of the gland has given the pathologist much trouble in the attempt to correlate the pathology with the clinical type. In consequence, the same thing has happened as in the case of the clinical classification—a great variety of pathological forms has been created to conform to the clinical forms. But if the pathologist accepts the histologic criteria used commonly today for the diagnosis of “hyperthyroidism” or “toxic adenoma,” namely, *epithelial hypertrophy* and *hyperplasia* (the so-called Basedow-adenoma metaplasia of the thyroid parenchyma) he falls at once into difficulties, for he will have sent to him thyroids, goiters and adenomas presenting on the most thorough examination no evidence of any parenchymatous hypertrophy or other condition of the thyroid secreting parenchyma that may not be found in the thyroids, goiters, or adenomas of other individuals who have never presented any symptoms of hyper- or dysthyroidism. The nodular and adenomatous goiters without recognizable epithelial hypertrophy on microscopic examination but that were associated clinically with a slightly increased metabolic rate or relatively slight cardiac or nervous instability have in particular given trouble to the pathologist. He finds further that there are as many transition stages pathologically as there are clinically.

It is generally stated in the literature that the pathological changes in the thyroid bear a definite relationship to

the clinical criteria for certain types. If the classic triad of exophthalmic goiter is present in well-marked degree, in association with an increased metabolic rate and the nervous syndrome, the pathologic changes expected to be present are those of a diffuse parenchymatous hyperplasia and metaplasia with total absence, or marked decrease of the colloid. When these are found the pathologist has no hesitation in making a pathologic diagnosis of true or typical Graves' or Basedow's disease (*struma parenchymatosa hypertrophica*), the “Basedow adenoma” of some of the continental writers. In other cases the parenchymatous hypertrophy is not diffuse but is focal in character, although precisely the same symptomatology has been presented, areas of colloid-bearing follicles are scattered through patches of hypertrophic follicles containing no colloid. Such cases have been regarded by some pathologists as representing either early, mild, moderate or incomplete cases of Graves' disease. The greatest difficulty presents itself in those cases in which with precisely the same symptomatology *no* epithelial hypertrophy can be found in the thyroid which shows a diminished, normal or increased colloid content. Some pathologists have attempted to get around this difficulty by assuming a degree of hyper- or dysfunction not intense enough to reveal itself in epithelial changes that are recognizable microscopically. If the presence of a goiter associated with an increased metabolic rate be taken as the essential diagnostic criterion of hyperthyroidism either with or without slight nervous or cardiac symptoms, or if the latter alone are regarded as sufficient criteria for

the diagnosis of thyroid disease, as is the practice of some physicians, the pathologic changes found in the resected thyroid may be those of a diffuse or nodular colloid goiter, or an adenomatous goiter, either with or without discoverable parenchymatous changes, or in some cases there will be found a malignant neoplasm of the thyroid, or inflammatory changes only, extensive so-called ligneous thyroiditis, tuberculosis, extensive hemorrhage, or more rarely syphilis (all frequently diagnosed as "secondary" Graves' disease, toxic goiter, toxic adenoma, hyperthyroidism, thyreosis, hyperfunctioning adenoma, etc.) In the adenomatous goiters removed on a diagnosis of "toxic adenoma" either the adenoma or the thyroid tissue proper may show diffuse or focal epithelial hypertrophy, or none at all. In many of these poorly-defined cases of so-called secondary Graves' disease the pathological criterion of epithelial hypertrophy as the infallible pathognostic entity underlying hyperthyroidism or toxic dysthyroidism cannot be found on the most thorough and careful examination. In these cases in which a true Basedow epithelial hypertrophy cannot be found the pathologist is thrown back upon the assumption of errors in diagnosis, or the adoption of new pathologic criteria, as the occurrence of necroses and other degenerative changes in the thyroid parenchyma, or to the development of new theories of *non-Basedowian* types of hyper- or dysthyroidism, or even be led to doubt the primary thyreogenic origin of Basedow's disease. He is perplexed still further by the fact that both the epithelial hypertrophy and similar degenerative changes may be

found to occur in the thyroids of individuals who were not suspected clinically of thyroid hyperfunction or dysfunction. With the greatest care in the pathological study, and with the examination of sections from tissue blocks taken from all parts of the gland there frequently occur such discrepancies between the clinical diagnosis and the pathological findings in so far as the occurrence of characteristic epithelial changes are concerned. Moreover, we have no positive knowledge of the exact relationship existing between the histologic appearances of the thyroid epithelium and its functional activity. It may be asserted, therefore, that at the present time we possess no histological criteria, as far as the *thyroid epithelium* is concerned, that give a pathologic unity to all of the clinical forms of thyroid hyper- or dysfunction.

When we turn to a consideration of the various theories of etiology of Graves' disease, toxic goiter and toxic adenoma, we find, likewise, no general acceptance of any etiology that will give a clinico-pathological entity to all of the forms of primary and secondary Graves' phenomena. The old *hematogenic* theory was long ago abandoned, the *neurogenic theory*, dating from 1848, has appeared in various forms, as the *bulbar*, *constitutional-neuropathic*, and the *sympathetic*, but no definite pathologic proof has been offered for either. The *mechanic theory* yielded to the *chemical theory* about the year 1866, and the latter has developed into the present day theories of *hyperthyroidism*, *dysthyroidism* and *thyreotoxicosis*. Finally, the most recent theory of the pathogenesis of Graves' disease is the *thymogenic*

which holds that the point of origin of this affection is to be found in *thymic hyperplasia*. Of these various theories concerning the etiology and pathogenesis of Graves' disease, the four, the *thyrotoxic*, the *sympathetic*, the *constitutional-neuropathic* and the *thymogenic* hold the stage at the present time. It is outside of the limits of this paper to discuss these four theories around which such an active polemic is being carried on at the present time. Particularly in this country owing to the views of Plummer has this discussion waged around the relationship of "toxic adenoma" to exophthalmic goiter. Plummer holds that they are two separate diseases with entirely different clinical manifestations and histological changes, different courses and showing different reactions to iodine therapy. He holds that toxic adenoma is a pure hyperthyroidism, while exophthalmic goiter is the result of the action of two factors, both hyperthyroidism and dysthyroidism. The conception of "toxic adenoma" has been accepted to a much greater extent by the clinicians of America than by those of Europe but even here opinion is divided. The fact of greatest importance, however, that in spite of the enormous opportunity afforded in America for both clinical and pathological study of all of these various affections of the thyroid the chief American writers upon the subject, those from the Mayo Clinic, Marine, and others have apparently failed to see the constitutional background underlying these conditions and have concerned themselves only with the theory of hyper- or dysfunction as the etiological factors.

To the writer's mind the most interesting and striking pathologic feature of the Graves' disease thyroid is the *constant presence of hyperplastic lymph nodes with large germinal centers showing the characteristic lymphoid exhaustion of the thymico-lymphatic constitution*. This feature of thyroid pathology in the glands resected for symptoms of exophthalmic goiter and "toxic adenoma" is so constant and striking that it is amazing that American writers on the pathology of these conditions who have had access to a large goiter material, as at the Mayo's, should have failed wholly to mention it. Only MacCallum among American writers notices this remarkable and constant finding in the exophthalmic thyroid. In his 1924 edition he says "Definite lymphoid nodules are often found scattered through the gland, an appearance which, while fairly characteristic of this disease is rarely if ever seen in the normal thyroid." He does not ascribe any diagnostic value to this finding, and although he has found in all of his autopsies on cases of exophthalmic goiter that the thymus is hyperplastic and that the lymph nodes are usually enlarged, particularly these in the neck, he does not recognize the constitutional background for these findings. In the illustrations showing the micropathology of the thyroid in exophthalmic goiter, found in American textbooks not one including MacCallum shows a hyperplastic lymphoid nodule. It is evident, therefore that this constant and striking finding made no impression upon the authors as bearing directly upon the problem of Graves' disease.

On the other hand in Europe a



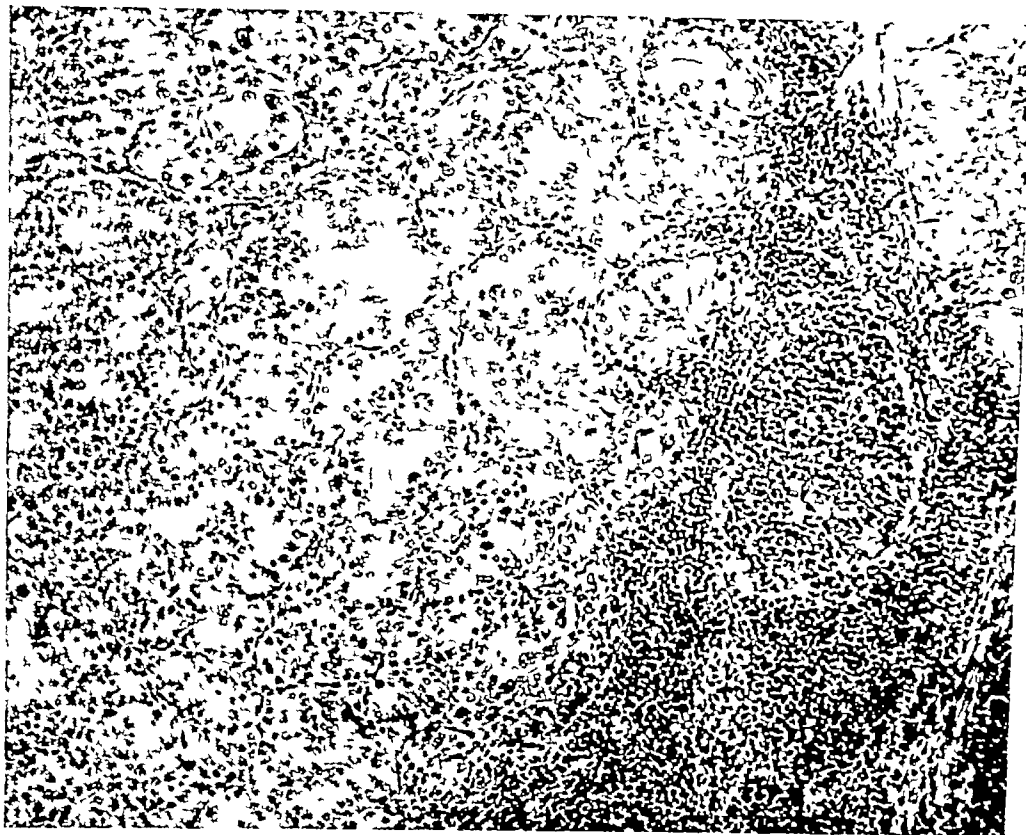


FIG. 1 Typical untreated exophthalmic goiter Epithelial hypertrophy, Absence of colloid and hyperplasia of lymphnodes

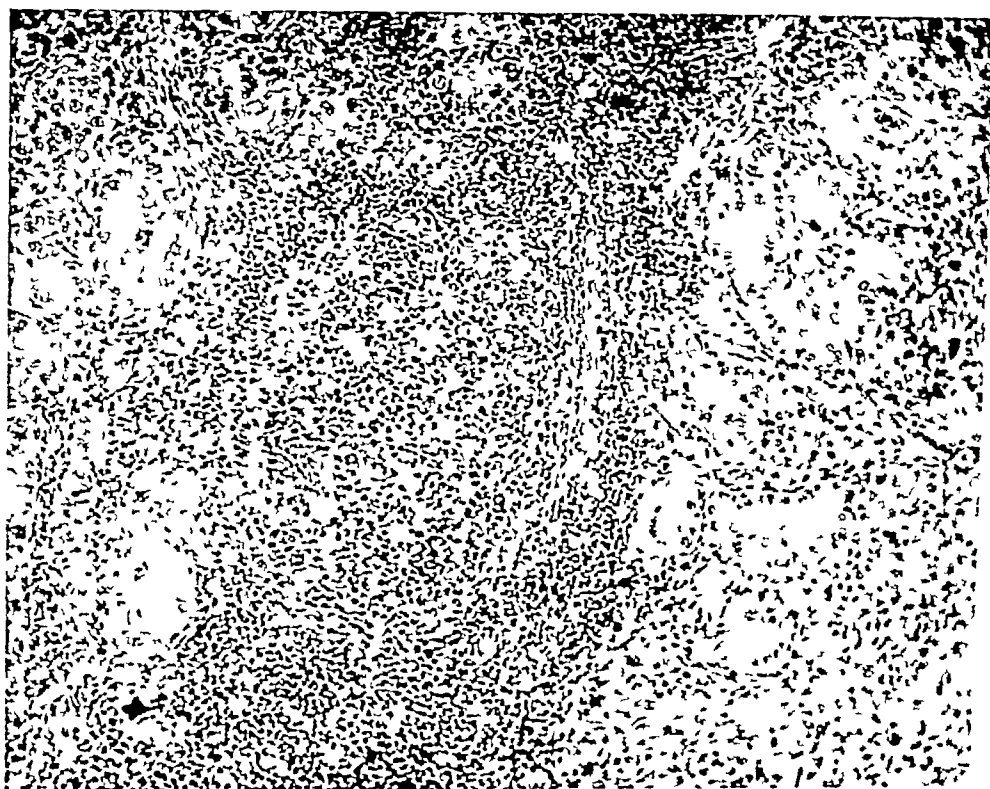


FIG. 2 Typical untreated exophthalmic goiter Epithelial hypertrophy and hyperplastic germinal center



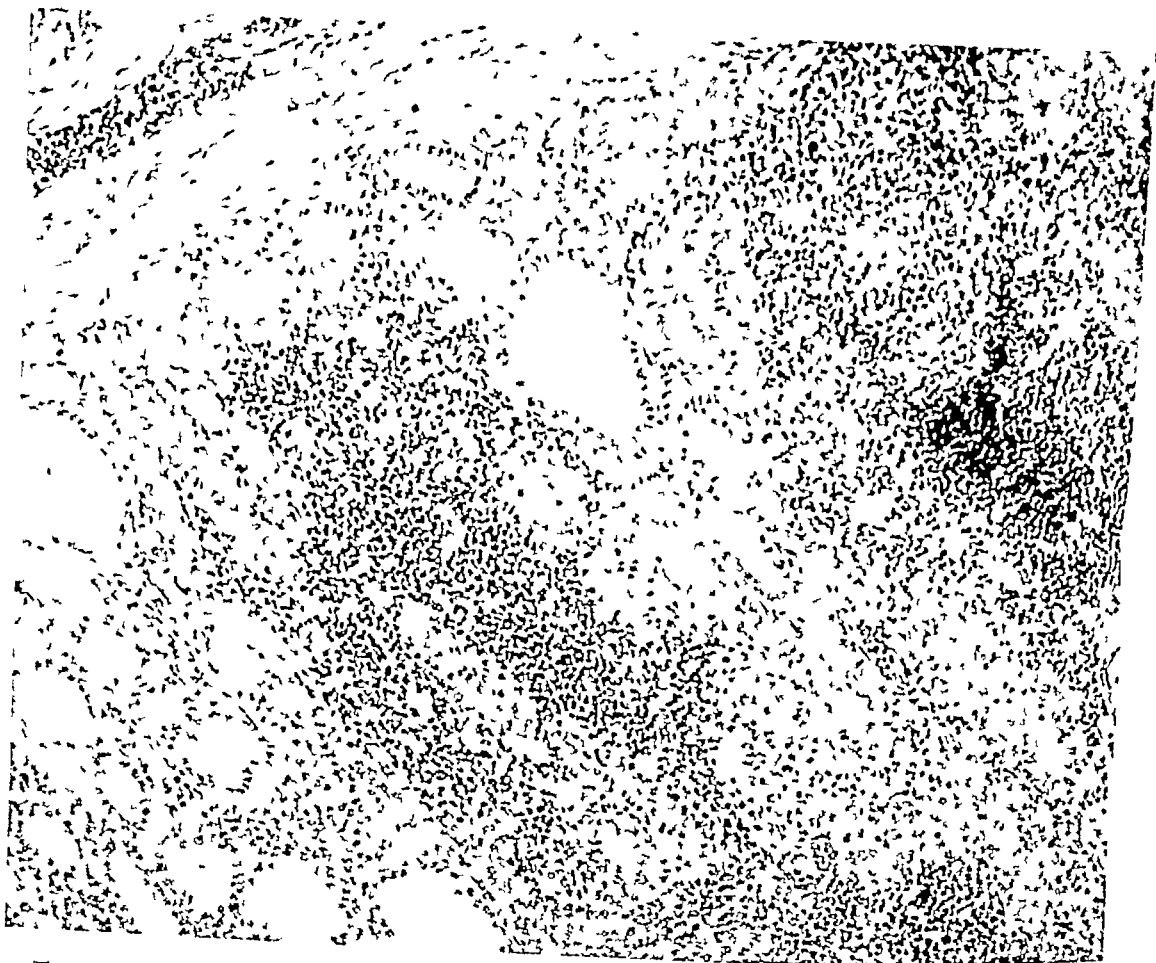


FIG 3 Iodized exophthalmic goiter Thin watery colloid in some follicles, some epithelial hypertrophy persistent around the lymphnodes



FIG 4 Higher power field from same case as preceding Iodized exophthalmic goiter

It will be seen from the above table that 154 thyroids out of the 976 thyroidectomies showed epithelial hypertrophy, either diffuse or focal with lymphoid hyperplasia, while 247 showed lymphoid hyperplasia, either with or without epithelial hypertrophy (93 without)

As to the correlation of the pathologic findings and the clinical symptoms, all of the goiters showing diffuse Basedow's with lymphoid hyperplasia were diagnosed as exophthalmic goiter, Graves' disease or hyperthyroidism, while the diagnoses of exophthalmic goiter, Graves' disease, hyperthyroidism, toxic goiter or toxic adenoma were applied to the adenomatous nodular and colloid goiters showing lymphoid hyperplasia either with or without epithelial hypertrophy. The term "toxic adenoma" was used in the University Clinic only during the last year or two of the period to which this material belongs. As far as could be learned from the rather meager histories other signs of the Graves' (thymico-lymphatic) constitution were present in the majority of these cases. An additional pathological finding confirmatory of this view is the presence in many cases of *cervical thymus lobes* showing marked hyperplasia of the medullary portion with numerous and large corpuscles of Hassall. As the majority of these cases occurred before the days of routine basal metabolism estimations it can only be said that a marked increase was shown in the metabolic rate of the relatively few cases showing both epithelial hyper-

trophy and lymphoid hyperplasia in which this procedure had been carried out. The symptoms determining the clinical diagnosis were exophthalmos in 50 per cent of cases, soft pulsating goiter (in 80 per cent), marked tremors (100 per cent), tachycardia (100 per cent), nervous excitability (100 per cent), vasomotor disturbances (100 per cent), and exhaustion (80 per cent). In a relatively small number of cases of adenomatous nodular and diffuse colloid goiters without epithelial hypertrophy or lymphoid hyperplasia, clinical diagnoses of exophthalmic goiter ("mild," "suspected," "incipient," etc.) hyperthyroidism or toxic adenoma had been made. These diagnoses were based upon vague histories of "nervousness," "palpitation" and increasing "weakness" in association with an enlarged thyroid. In another group appearing within the last years of the given period a number of cases of undoubted hyperiodism were also diagnosed clinically as exophthalmic goiter, toxic adenoma, hyperthyroidism, etc. which on microscopical study showed thin watery colloid, fatty epithelial changes and no epithelial hypertrophy or lymphoid hyperplasia. In a certain number of such cases marked atrophy of the follicular epithelium was present suggesting a condition of hypothyroidism which was borne out by various symptoms in the patient.

In the 1000 autopsies studied in which the thyroid was examined routinely there were

Adenomatous Goiter with Hypertrophy of the Epithelium	12
Nodular Colloid Goiter with Lymphoid Hyperplasia without Epithelial Hypertrophy	21
Colloid Hyperplasia (Iodism) with Lymphoid Hyperplasia without Epithelial Hypertrophy	6
Carcinoma of Thyroid with Lymphoid Hyperplasia but no Epithelial Hypertrophy	1
	94

The two cases of carcinoma of the thyroid were diagnosed clinically as exophthalmic goiter, as were the six cases of hyperiodism. In about 50 per cent of the nodular colloid goiters and the adenomatous colloid goiters the diagnosis of hyperthyroidism had been suggested, in the other 50 per cent it had not been diagnosed. In all of the 94 cases with lymphoid hyperplasia of the thyroid examined at autopsy as well as in the 35 autopsy cases of exophthalmic goiter with diffuse epithelial hypertrophy and lymphoid hyperplasia, there was found associated the general pathological picture of the thymicolymphatic constitution. Hyperplastic or persistent thymus, general enlargement of the lymph nodes and spleen, hypoplasia of the adrenals, heart and aorta with other morphologic stigmata of the constitution.

That the lymphoid hyperplasia constitutes the most constant histological feature in the thyroid of individuals belonging to the Graves' constitution type is shown by the examination of resections made at long intervals of time. In one case of typical Graves' disease a partial resection showed a diffuse Basedow epithelial hypertrophy without colloid but with hypoplastic lymph nodes. Fifteen years of so-called "recovery" elapsed when there was a sudden return of symptoms in a mild degree. Another resection showed no epithelial hypertrophy, the colloid was abundant and normal in appearance, but the primitive lymph nodes were hyperplastic (Fig 8). In another individual with classical symptoms of Graves' a partial resection showed an adenoma with marked lym-

phoid hyperplasia but no epithelial hypertrophy. A clinical "cure" followed lasting about two years, when with return of the symptoms another resection was performed, with the same results. In all this patient has had seven partial thyroidectomies extending over a period of eighteen years, and in each resection the pathological picture is the same. Marked lymphoid hyperplasia, abundant colloid, degenerating fetal adenoma, without epithelial hypertrophy. This patient shows all of the stigmata of the thymic-lymphatic constitution in a marked degree. There can be, of course, no cure for any primary constitutional defect, the stigmata of the latter will persist. It is apparent from our study that the constitutional defect of the thymic-lymphatic (Graves') constitution underlies every case of exophthalmic goiter and "toxic adenoma." Constitutionally they show the same pathologic entity. An adenoma of the thyroid, aside from its size and mechanical effects, is clinically important as far as so-called *toxic* symptoms are concerned only when it is associated with the thymic-lymphatic constitution. My assertion, therefore, is that exophthalmic goiter and "toxic adenoma" possess the same pathologic constitutional entity. This, of course, does not explain the whole problem of so-called hyper- and dysthyroidism. What determines the symptoms referable to the thyroid in this constitution, whether *thyrotoxic* or *thymogenic* remains to be solved, but it is certain that the thyroid is not the *whole* story, and not the *primary* pathogenic factor. While the total number of thyroids (2011) studied as to the occurrence

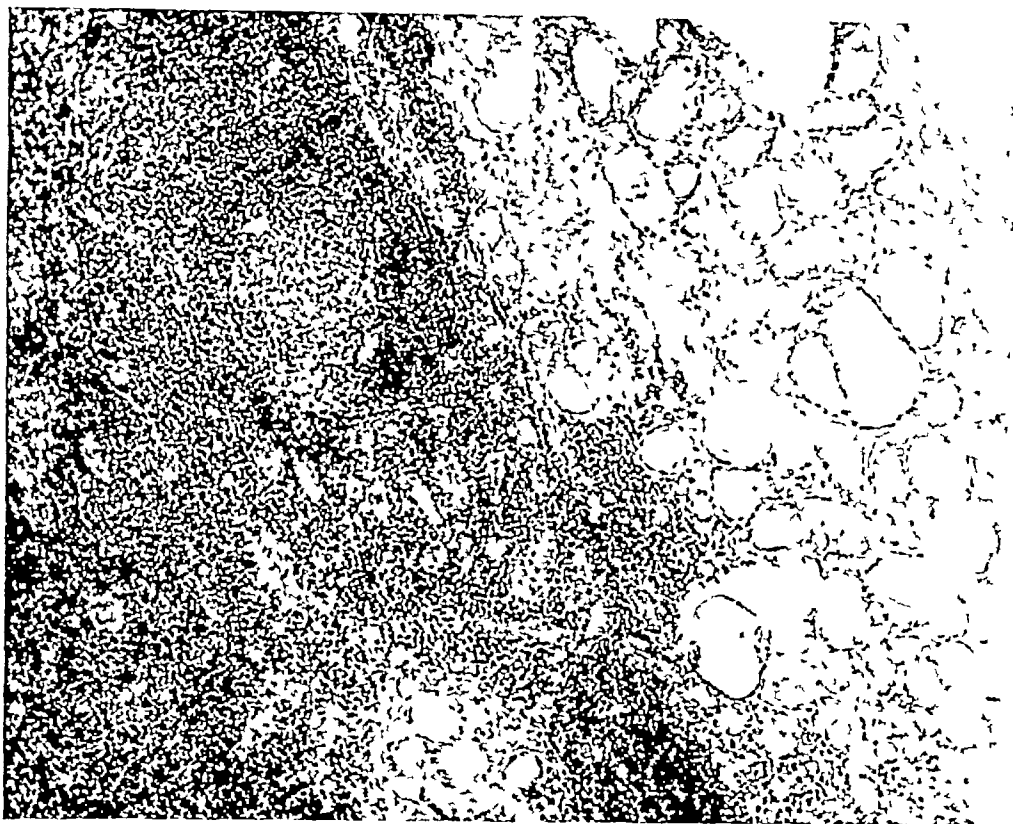


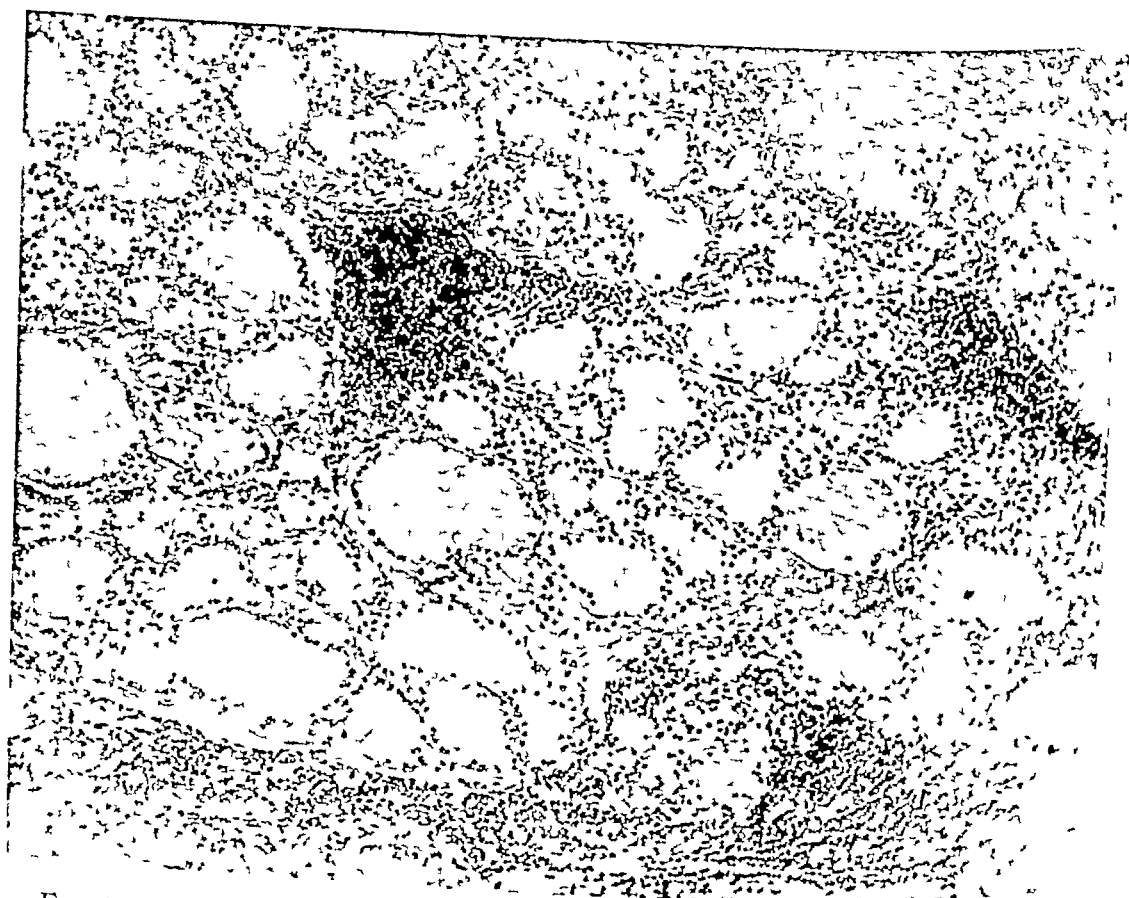
FIG 5 Over-iodized exophthalmic goiter (Lugol's taken for 6 weeks) Thin watery colloid, no epithelial hypertrophy, atrophic follicles, marked lymphoid hyperplasia



FIG 6 Hyperiodism Over-iodized Graves' constitution Thin watery colloid No epithelial hypertrophy Atrophy of follicles Marked lymphoid hyperplasia with lymphoid exhaustion of follicles Lugol's was taken in usual dose three times daily for three months



FIG 7 High power view of hyperplastic lymph follicles from preceding, showing lymphoid exhaustion of germinal center



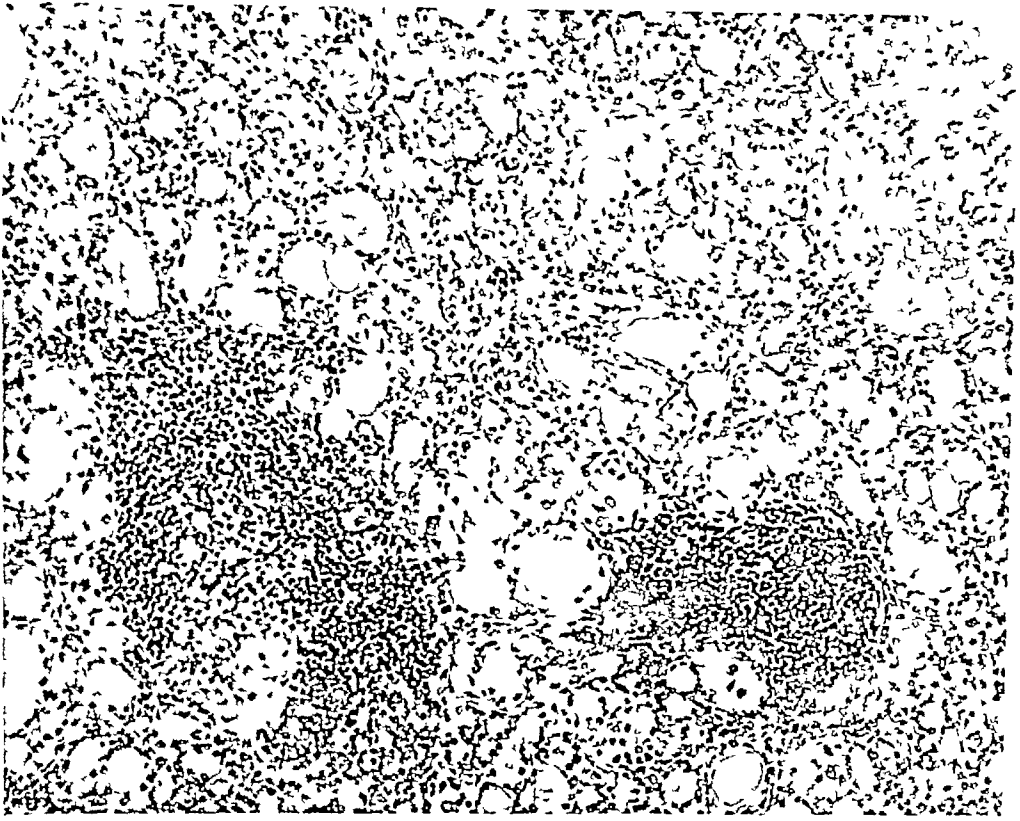


FIG. 9. Clinical diagnosis "Toxic Adenoma." Multiple adenomas of fetal type, with hypertrophic lymphnodes and germ centers throughout adenomas. Pathologic diagnosis "Adenoma with Graves' Constitution."

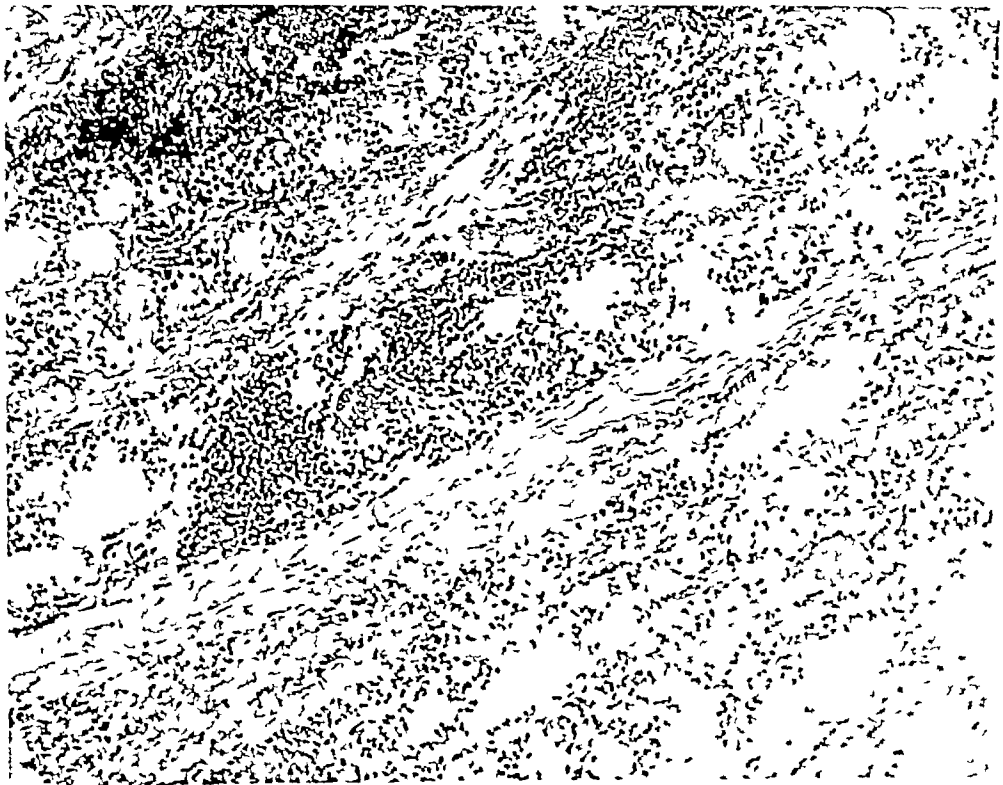


FIG. 10. From same cases preceding. Compressed and atrophic thyroid tissue and fibrosis between adenomas. Hyperplasia of lymphoid tissue. Graves' Constitution.

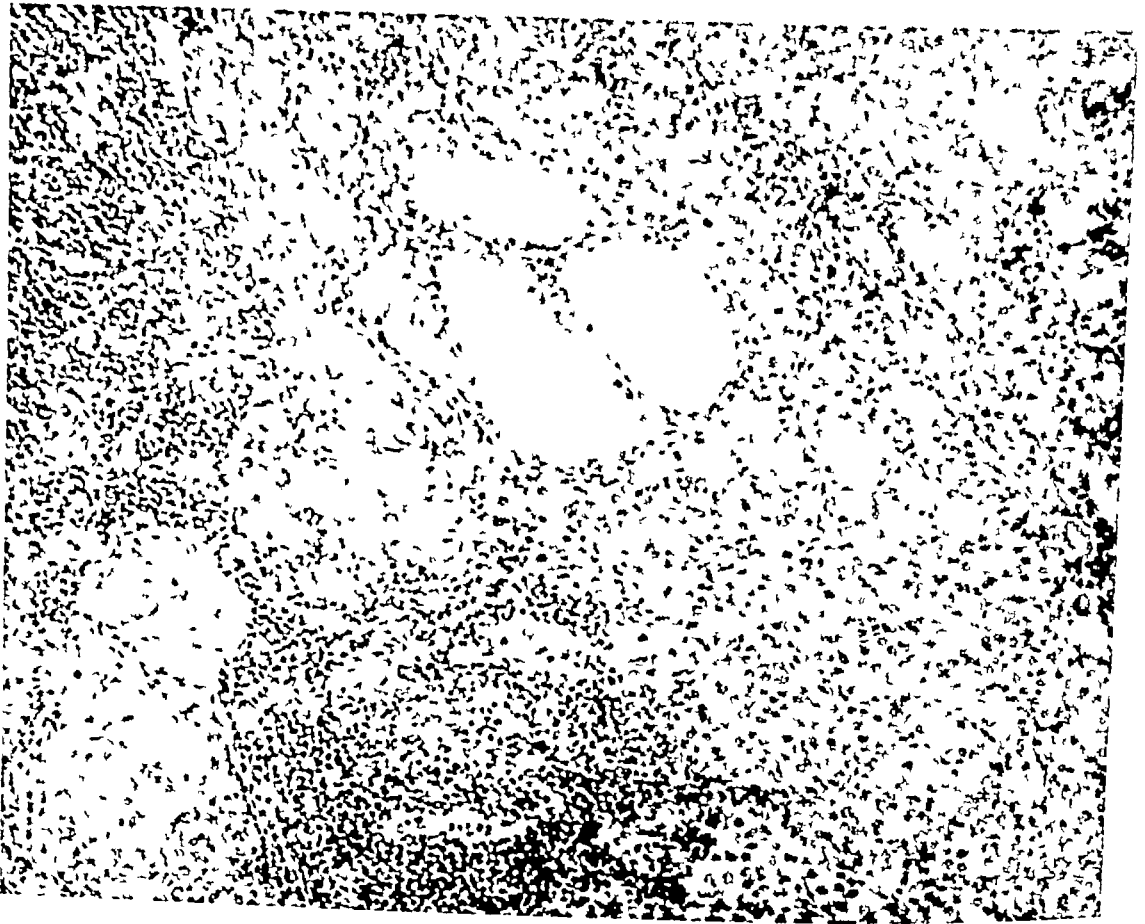


FIG 11 Iodized adenoma with Graves' constitution Thin colloid Iodine hypertrophy of adenoma follicular epithelium



FIG 12 Adenoma in exophthalmic goiter with over-iodinization (6 weeks) Marked lipoidosis of adenoma epithelium (left), thyroid tissue on right of adenoma capsule shows picture of iodized exophthalmic goiter Graves' constitution adenomatous goiter, over-iodized





FIG 13 Hyperplastic cervical thymus. These are frequently found in operative material and are always associated with the Graves' constitution, both the exophthalmic form and the toxic adenoma. In the autopsy cases of both of these conditions the main thymus of the upper mediastinum shows always the same hyperplasia.

of hyperplasia of the lymphoid tissue in the thyroid and other stigmata of the thymic-lymphatic constitution may not be considered sufficiently great for such decided conclusions, yet so much confirmatory evidence is found in the literature that I have no hesitation in stating them as follows:

1. Exophthalmic (Basedow's) goiter, "toxic goiter," "hyperthyroidism" and "toxic adenoma" present always the pathologic picture of hyperplasia of the primitive lymph nodes of the thyroid, hyperplasia of the thymus and other anatomic stigmata of the thymic-lymphatic constitution. In addition, they present certain constitutional peculiarities of their own kind. Not all

cases of thymico-lymphatic constitution will present the Graves' disease syndrome, although all cases of the latter will possess the chief morphologic stigmata of this constitution.

2. All forms of Basedowian or Graves' symptoms represent the abnormal reactions of a primary pathologic constitutional anomaly.

3. Basedow's or Graves' disease, "toxic goiter" and "toxic adenoma" are *pathologic reactions* potentially predetermined in the individual at birth by virtue of his constitutional anomaly.

4. The development of the Basedowian or Graves' symptoms in so far as the thyroid is concerned is but the expression of abnormal reactions of



this constitutional anomaly to the conditions of the life of the individual. Only those possessing this constitutional anomaly will ever develop the so-called hyperthyroid or thyreotoxic symptoms. The potentiality may, however, remain "*latent*" or quiescent during the whole or a large part of the potential's life. The clinical and pathologic stigmata of the potential Graves' disease constitution may, however, be easily recognized in this individual.

5 There can be, of course, no *cure* for the constitutional anomaly on which the development of "hyper" or "toxic" symptoms depends. These abnormal reactions may, and usually do, remain below the clinical horizon until called forth—in what way or by what mechanism we do not yet fully understand. It is evident however, that the thyroid gland is not the chief pathogenic factor in these various clinical syndromes usually referred to this

organ, it is but an incidental complication or sequela, comparable to the participation in abnormal reactions of other organs and systems dependent upon the constitutional anomaly.

6 The most important histologic criterion of Basedow's disease, and the allied clinical conditions of toxic adenoma, hyperthyroidism, etc., as far as the thyroid itself is concerned, is the presence throughout this gland of hyperplastic primitive lymph nodes with germinal centers showing lymphoid exhaustion. Their presence determines the existence of the underlying constitutional anomaly. This potential Graves' constitution may be recognized in the thyroid of very young children.

7 To this constitution I have preferred to apply the term "Graves' constitution." It is the underlying pathologic and clinical entity of exophthalmic goiter, toxic goiter and toxic adenoma.

## Editorial

### COMMON SENSE AND SO-CALLED LIFE EXTENSION

It is unfortunate that many journalistic statements of the great results accomplished by modern scientific medicine have so emphasized the fact of the increase in the average longevity, from 35 years in 1880 to 42 years in the male and 47 years for the female in 1910, to 58 years in 1920, that they have been led to broadcast prophetic estimations of the power of preventive medicine to bring about still further increases in the average duration of life, to 65 years in 1930 and to 75, 80 and still higher in future decades. One enthusiastic medical lecturer upon this subject has been so wrought by the spirit of euphoric prophecy as to declare that average life-limits of 125 or even 140 years are not unattainable goals for the human race in the next century or two. Such assertions as these have no scientific foundation, and in fact are wholly contradictory to the actual knowledge we possess in regard to the nature of old age and the natural limit of life in the individual. Moreover they have had the unfortunate effect of producing in the layman's mind the belief that it is the *individual life-limit* that is capable of extension to such high figures. *Average* is thus interpreted as *individual* particularly in this connection and *expectancy of life* at any given age confused with individual

life limits. Further, has any one of these zealous advocates for life-extension ever paused to consider what the effects of an average longevity rate of 65 years would mean to the race and to society at large? The actual truth of such a state of affairs would be the presence in every community of a greatly increased group of dependents non-productive, useless more or less uncomfortable and unhappy individuals, who are burdens to others as well as to themselves, and what possible advantage can be gained by increasing so greatly the number of cases of senile "second childhood." For the extension of the average longevity does not mean the deferring or abrogation of senescence—the manifestations of old age will continue to take place in the same decades and in the same years—and the only thing accomplished by the extension of the average duration of life will be ultimately an increase in the number of senile individuals persisting in the community. The *secondary pathology* of old age has been confused with the *normal involution* changes of senescence. We may reduce the dangers and the frequency of the former but only long evolutionary periods of the action of forces beyond our control can alter the latter process. There has been created a very false conception of old age. Medical writers have considered it to be a *disease* a *pathology*

Of Every 100 Human Beings Born	According to Hufeland (1800)	According to Silbergleit (1900)
Living to the 10th year	50	65
" " " 20 "	30	60
" " " 30 "	20	58
" " " 40 "	14	55
" " " 50 "	9	40
" " " 60 "	6	12
" " " 70 "	4	8
" " " 80 "	2	4

matter of fact the expectancy of life for individuals over 80 years of age has actually been lowered since 1910, as shown by the following table —

EXPECTATION OF LIFE IN YEARS

Age	1910		1919-20	
	Men	Women	Men	Women
52	18 96	20 33	19 91	20 79
57	15 73	16 80	16 51	17 27
62	12 83	13 68	13 38	14 01
67	10 24	10 88	10 56	11 11
72	7 95	8 47	8 17	8 66
77	6 04	6 42	6 17	6 61
82	4 57	4 80	4 53	4 98
87	3 51	3 64	3 21	3 70
92	2 73	2 72	2 10	2 63

The saving of life has, therefore, been confined chiefly to the early and middle years of life, while the individual lives have not been extended into a later old age, but, on the contrary, the expectancy of life for those who reach the eighties appears to have actually decreased. It does not appear either possible or probable under the present conditions that the average longevity can be raised to the heights prophesied by the over-zealous advocates of life extension. If the number of individuals reaching extreme old age is actually diminishing and not increasing, the fear as to an accumulation in society of senile de-

pendents in second childhood may not be realized. We are still faced, however, with the doubtful question of the value of the increasing number of lives saved in the early years of life. To what extent do those saved to grow up to maturity represent the fit or the unfit? We can hardly avoid the conclusion that a large number of those who through modern medical science are classed as *saved lives* must represent an inferior value of protoplasm, and the saving of these to grow up to maturity when they can reproduce their own kind cannot work otherwise than as a hindrance to the highest development of the species. These are questions that cannot be dogmatically answered at the present time, but if scientific deductions have any value there are certain results that must be counted among the possibilities. If the dangers of the environment can be so reduced that we save increasing numbers of the unfit as well as the fit, and if we extend the later years of life so as to increase the number of dependents in their second childhood, there may be brought about through the action of evolutionary factors an actual shortening of the biologic life limit instead of its prolongation. It

the struggle for existence of the species is made easier, if more individuals reach the reproductive age, and more children are born to survive, if the period of caring for the progeny is shortened, theoretically the next evolutionary period should see a shortening of man's normal life limit. This result, of course, is not so vital to us in this present phase of evolution of man as is the increase in the number of unfit and dependent. Nevertheless, if we are interested in the future development of the race we should be concerned as to both of these possibilities. Both can be obviated by an intelligent breeding of the human race, in the limitation of birth number, and better selection of parents, as well as in the prevention of both extrinsic and intrinsic pathological conditions in the individual. Old age is as normal a biologic entity as is the period of development or that of maturity. The processes of growth and involution are inseparable, they go hand in hand from the time of the fertilization of the ovum and the development of the embryo. Throughout the whole period of development there are localized involutions of organs and tissues necessary to the production of the mature organism. These minor senescences are identical in nature and function with the major involution, old age. The placenta is a senile structure at birth, it has played its function and is discarded, as is later the senile organism as a whole when it has completed its functional rôle of reproduction and preservation of the species. Old age, the major involution, is but a complex of minor organ- and tissue- involutions that have for their purpose the getting rid

of a useless machine. Old age is normal, physiologic, intrinsic, it cannot be prevented or deferred. It is inevitable. Rejuvenation is impossible. Biologic death will take place when the individual energy-charge has become so weakened that one of the vital functions, usually the cardiovascular, cannot be kept at the level necessary for the maintenance of the life-processes. The time of life, measured in years, at which this will occur is fixed in the germ plasma and cannot be altered. The essential involution changes will proceed, no matter what the environment may be. To this fact it is wisdom to adjust ourselves. We must all take the downward path toward an ultimate physiologic death. If our individual resistance is unusual and our environment exceptional we may escape an earlier pathologic death. But why should we wish it if that means a decade or so of uselessness and dependency. The mental and spiritual functions of the body are the last to decay, but in the majority of individuals the decline of cerebral function begins in the 65-75 year and declines very rapidly after this time. Except in rare cases, by virtue of individual inheritance, the period of second childhood becomes instituted after the 75th year. Three score years and ten constitute an ideal desideratum of the length of life for the average individual, for up to this time life may still contain much that is good and worth while. Fortunate then is he, who after a life well spent is removed from the scene by some of the pathologic factors of the environment before the sad days of extreme old age bring to him unhappy dependency.

## Abstracts

*A Biochemical Approach to the Study of Personality* By GILBERT J. RICH, Ph D  
(*Jour. of Abnormal and Social Psychology*, 1928, XXIII, p 158)

The scientific study of personality is today one of the outstanding problems of psychiatry as well as of psychology. But when one looks for facts regarding personality or methods of measurement and diagnosis of personality traits, the search is almost in vain. During the last two decades one phase of personality, intelligence, has been intensively studied by psychologists, and this study has been fruitful from several aspects. A series of test scales has been devised which serve as more or less accurate measures of a person's general intelligence as well as his special abilities and disabilities, and the results obtained by mental testing have led to considerable insight into the nature of intelligence and the hereditary developmental factors involved in it. Other phases of personality have not fared so well. This fact is reflected in the frequently repeated statements that intelligence is not the whole story, and that mental tests give a very one-sided and distorted view of the person who is tested. Intelligence is only one phase of the multiplicity of behavior traits which make up the integrated whole which we call personality. Attempts have been made by psychologists in recent years to use methods similar to those employed in intelligence tests in the study of non-intellectual traits. Up to the present time these studies have progressed very slowly, and there are not as yet any adequate tests of traits other than intelligence. Whether or not it is possible to study and measure the non-intellectual traits by purely psychological methods cannot be definitely said at this time. It would seem, then, that in the absence of psychological methods the time is ripe for a biologic approach of the

problems of personality, for a study of the relationship, if any, which may exist between an individual's behavior and his biologic characteristics. Morphologic factors have been considered in the last few years in a series of studies. Psychologic factors have occasionally been dealt with in connection with the extreme traits found in mental disease, in such studies as those of Raphael on the physiologic level in dementia precox and those of Ludlum and McDonald on the balance between vagus and sympathetic tonicity in mental disease. With the growth of better knowledge of the action of the endocrinal glands the relation of personality to endocrine function has become a matter of popular as well as of scientific interest. It does not, however, lend itself to quantitative experimental investigation at the present time, owing to the lack of methods for measuring any but the more extreme changes in endocrine functioning. All branches of physiology are today tending to express themselves in biochemical terms, and an attempt is now made to consider directly any biochemical factors which may be connected with characteristics of personality. The author has attempted to investigate this problem by obtaining from a group of the same individuals ratings upon a few personality traits and biochemical determinations upon certain features of body metabolism, and then correlating the results to ascertain what, if any, relationships may be obtained between the mental and chemical characteristics. As a result of his investigations the writer concluded that preliminary experimentation indicates tendencies for the following relationships to hold. The least excitable individuals tend to have the most acid urine and saliva, while more excitable persons tend toward neutrality or alkalinity of their fluids. The least aggressive subjects appear to excrete the great-

est amounts of acid as measured by the formol titration and to have the highest alkali reserve of the blood, while more aggressive individuals seem to show opposite characteristics. Emotional excitability tends to bear an inverse relationship to the presence of creatinine in the blood and its excretion in the urine. Phosphorous metabolism appears to be bound up with personality in some way, but the details of the relationship are not yet clear. The above tendencies must be accepted and interpreted cautiously until further proof is forthcoming, as it was not possible completely to control the experimental situations. The degree of the relationships found to exist between chemical determinations and personality traits is that expressed by coefficients between 120 and 130. The results obtained in the present study justify further experimentation along the same lines.

*Changes in the Peripheral Circulation Accompanying "Tobacco Angina"* By ELAINE P. RALLI AND B. S. OPPENHEIMER (Proc. Soc. f Exper Biol and Med, October, 1928, p. 8)

It is now fairly well established that coronary artery disease, occlusion and consequent myocardial infarction constitute one of the pathological conditions associated with the syndrome, angina pectoris. There is, however, a great diversity of opinion as to the mechanism of this symptom-complex, the probability is that typical angina pectoris is due to a single mechanism. There are several well recognized exciting causes of angina such as physical effort, emotional excitement, exposure to cold or to fresh air, overeating, and in some patients tobacco smoking. The authors have observed a very few patients, beyond middle age, predisposed to angina pectoris, in whom the attacks could be provoked very promptly by smoking a cigarette. The attacks of pain induced by smoking were relieved by the administration of a nitroglycerin tablet dry under the tongue, but were not relieved by a tablet similar in appearance but not containing any nitroglycerin. The relief of pain was, there-

fore, not due to a psychic factor, no attempt was made to substitute any form of smoke other than that of tobacco. These few patients, therefore, offered an opportunity to study the peripheral circulation before, during and after an attack of angina pectoris. This was done by making observations of any change in limb volume by means of a plethysmograph on the left arm, and simultaneously of the systolic and diastolic blood pressures in the other arm by the auscultatory method. Observations were made on 6 patients, all giving a history of precordial pain, also on 2 normal individuals, one male and one female, as controls. One patient 45 years of age, formerly a heavy smoker, with elevated resting blood pressure, would experience a typical attack of angina pectoris following 4-5 deep inhalations of a cigarette (Deep breathing alone would excite an attack). Each attack consisted of precordial pain, radiating into left arm, with angor animi, ashy color, and cold perspiration. The pain was associated with a marked rise in both the diastolic and systolic blood pressure, and by evidences of peripheral vasoconstriction as registered by the plethysmograph. The peripheral constriction preceded the onset of pain by 15-45 seconds. There was a marked rise of systolic and diastolic blood pressure (of about 40 mm of mercury) which followed the peripheral vasoconstriction but just preceded the onset of pain. Following the administration of 1/100-1/50 grain of nitroglycerin tablet dry under the tongue, the plethysmograph would give evidence of peripheral dilatation which preceded the cessation of pain. The interval of time elapsing between the peripheral dilatation and the cessation of pain depended somewhat on the severity of the pain. Three separate sets of observations were made on this patient, and in each case the results were the same. In three of the 6 patients there was definite evidence that first peripheral vasoconstriction, and later a rise in arterial tension preceded the onset of pain. In 2 other cases there was evidence only of one elevation of systemic blood pressure, but not definitely of peripheral vasoconstriction. The sixth patient

refused to smoke, but exercise with a foot ergograph resulted in a rise in arterial tension with each attack of pain, but there was only slight evidence of peripheral vasoconstriction. There are, therefore, instances of patients predisposed to angina pectoris, in whom cigarette smoking induces a peripheral vasoconstriction, which precedes the onset of pericardial pain. At the same time an elevation of blood pressure was observed, so that it is reasonable to suppose that there was a general vasoconstriction, in which the coronary arteries may have taken part.

*Studies on Inhibition of Insulin Activity*  
By SAMUEL KARLITZ, PHILIP COHLN  
AND SYDNEY D. LEADER (Proc Soc  
Exper Biol and Med, October, 1928, p  
11)

This investigation on the inhibitory effect of blood on insulin activity was incited by the study in 1925 of a diabetic child with refractory periods to insulin. The work was done with rabbits. One physiologic or 3 clinical units of insulin were mixed with the substance investigated and incubated at 37° C from 1 to 2 hours, then injected subcutaneously into rabbits weighing 2 kilos, starved during the preceding 24 hours. Hourly blood sugar determination and clinical observations were made. The results summarized were as follows: 2-4 cc of human plasma caused hardly any inhibition of insulin action, 5 cc of human plasma caused moderate inhibition of insulin action, 10 cc caused marked inhibition, 15 cc. caused complete inhibition. 2 cc of centrifuged unwashed blood cells caused mild inhibition, 5 cc of the same caused marked inhibition, 5 cc of human plasma from diabetics caused almost complete inhibition, 2 cc cells from myeloid leukemia caused complete inhibition, 2 cc pus of case of empyema caused complete inhibition. The results suggest that there is something in human blood plasma which is more abundant in blood cells, more in diabetic blood than in normal human blood, and still more in leukemic cells and pus which inhibits or destroys the action of insulin. It is probably more abundant in blood of

patients with fever, leucocytosis, suppurative processes, or serum sickness, than in the normal state. The extent of inhibition is variable for individuals, but quantitatively proportional to the amount of blood used. The authors are of the impression that the inhibitory substance may be a proteolytic enzyme, because the inhibition is greater with blood cells than with plasma, greater with leukemic cells and pus than with normal cells, and because it seems to be stronger during fever or infection or after vaccine injection. Even more significant, in that it may be enzyme reaction, is the experiment in which the blood or pus heated at 57° for 1-2 hours no longer inhibited insulin action. Similar experiments with blood cells were not as convincing as was plasma or pus.

*Die Syphilitische Blutveränderung* By PROFESSOR FELIX KLOPSTOCK (Klinische Wochenschrift, September, 1928, p 1896)

The nature of the syphilitic blood change is still under discussion two decades after its discovery, as shown by the varying theories still supported by different groups of investigators. Three principal theories at present are: the physical-chemical theory, according to which its demonstration by means of organ-extracts is not an antigen-antibody reaction but a colloidal reaction between serum-colloids and extract colloids, the autoantibody theory which regards the cause of the alteration of the blood as due to the appearance of reaction-products against the body's own organ-lipoids, and the theory that the syphilitic blood change is an immune reaction against the spirochete invasion and owes its peculiar character to the chemical nature of the spirochete body itself. The immune reaction produced by the spirochetes of syphilis holds an individual position in several ways. The antibodies combine not with the whole substance of the exciting agent but only with its lipid portion, the lipid substances of the spirochetes are replaceable in serum reactions by organ-lipoids, the antibodies are through their respective antigens not sufficiently adsorbable, there arises therefore a blood change which can be

demonstrated by chemical and physical-chemical methods, the globulin of the serum is more easily precipitated by distilled water, the precipitate produced in lues-serum by nitric acid dissolves more slowly and with greater difficulty, the treatment of a leucic-serum with 33 per cent ammonia sulphate precipitates more thermostabile globulin than in normal serum. Above all, the colloidal-chemical state of the albumen complexes is so altered that the serum alteration can be demonstrated by methods of colloid chemistry through flocculation and precipitation reactions with given lipoids and balsam extracts. Klopstock has been able to produce + + + + Wassermann reactions in animals by the intravenous use of the dipeptides leucylglycin and glycylserin, the tripeptides diglycylglycin, glycylleucylglycin and one tetrapeptide alanyldiglycylglycin. After a few intravenous injections of a 1 per cent solution of these preparations there took place within two days a complete change of the serum reaction. In 5 experimental series

of 4 animals each a + + + + reaction was produced. In a second group of experiments in which albumin-substances were split up into polypeptides through tryptic digestion showed the property of producing a positive Wassermann in rabbit experiments. In the reagent glass mixtures of normal sera with amino-acids and polypeptides in varying concentrations gave constantly negative results. Not only lipid-substances but a group of albumin split products lead on intravenous injection to the production of a positive Wassermann. Klopstock is convinced that the changes in syphilitic blood serum are the result of the antigen produced by the spirochetes only. His view may be expressed as follows: The syphilitic blood-changes are produced by the spirochete invasion, their peculiarity as an immune reaction depends, not upon albumin-bodies, but upon lipid substances in the spirochetes which act as antigens and lead to the production of anti-bodies which enter into combination with the serum-albumin.



## Reviews

*Constitutional Inadequacies* An Introduction to the Study of Abnormal Constitutions By NICOLA PENDE, M.D., Professor of Clinical Medicine, Royal University of Genoa, Italy Translated by SANTE NACCARATI, M.D., Sc.D., Ph.D., Associated Professor of Nervous and Mental Diseases, New York Post-Graduate Medical School With a Foreword by GEORGE DRAPER, M.D., Assistant Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University, Chief of Constitution Clinic, Presbyterian Hospital, New York City Octavo, 270 pages, illustrated, Lea and Febiger, Philadelphia, 1928 Price in cloth, \$3.50, net

A new era in medical philosophy has been developing slowly but surely during the first quarter of this century almost unrecognized by the great mass of American practitioners, and ignored even by some of the teachers of medicine in our Medical Schools Particularly has American Surgery failed to recognize the importance of *constitution*, in its modern sense, in its relationship to disease and reaction to surgical procedures In England and in France a similar lack of progress in modern medical conceptions is apparent Italy, Germany and Austria have paid much more serious attention to the importance of the *human biotype* in diagnostic medicine, and a knowledge of human *biotypology* is there held to be an absolutely necessary premise for the proper understanding and interpretation of clinical problems Constitutional pathology is essentially a differential pathology, a pathology of the variations in disease-pictures presented by the special personality of the individual It is, therefore, essentially clinical medicine in its most complete form The medical practitioner of today if he is up to date in clinical and

close attention to both the endogenous and exogenous factors of disease Our modern advance makes this imperative, the modern development of studies in heredity, genetics and endocrinology has influenced clinical medicine in the most fundamental manner Medicine becomes daily more and more individualistic, and each individual patient must be studied, analyzed and interpreted clinically from the standpoint of his biotype Human patients represent either fairly distinct constitutional types or combinations (hybrids) of such types Herein lies the possibility of an enormous advance in the science of what has been called the "art of medicine" It is the taking to pieces of the individual make-up, the recognition of the morphologic, humoral and psychical elements of his constitution, and the evaluation according to the physiologic or pathologic worth of his individual components It is truly the "study of the whole man" Medicine is, therefore, just coming into its own—the study of man in his morphologic, chemico-humoral and psychological make-up Truly, this indicates that a new era in medical philosophy and practice is already here We see this exemplified in the examples set by Bauer, De Giovanni, Pende and other of the European masters of clinical medicine The present book, already published in German and Italian, makes available to English-speaking physicians the advanced doctrines of these great leaders of European medical thought Through the medium of this work the practitioner unfamiliar with the original writings of these great leaders in modern clinical medicine can be fully informed and enabled to keep abreast of the times The fundamental problems of the constitution are here embodied in a concise but complete form The interesting concepts, definitions, analysis and classification of individual biotype, details of personal study, and the principles of their

are all clearly presented. The study of this book will help the practicing physician not only in diagnosis and prognosis, but will supply him with practical criteria for successful therapy. Psychologists will find in it invaluable data on the constitutional potentialities leading to abnormal behavior. Dr George Draper, in his Foreword, says — "Professor Pende has been developing within his department of medicine a most effective unit for the study of the human constitution. The scale and completeness with which this 'Istituto Biologico' is conducted surpass anything of the kind elsewhere. So valuable is the work of this institute considered to be that it receives support both from municipal and state educational and public health funds. It will be quite apparent to the reader of this book that Pende has exhibited again that extraordinary capacity of the Italian savants to combine effectively, as did Leonardo in his matchless anatomical drawings, the detailed accuracy of the scientist with the perception and feeling of the artist. With his background of rich clinical and endocrinological experience he has presented a wealth of fine observation, and has advanced stimulating hypotheses for the explanation of those mechanisms which determine the appearance of the micro- and megalosplanchnic forms of Viola. The difficult and obscure subject has been presented in a direct and interesting fashion, and with a fine assurance. The conscientiousness, thoroughness, energy and perspicacity which Professor Pende, as a pupil of his great masters, De Giovanni and Viola, has put into his own efforts in the field of the human constitution, are reflected in this monumental work which marks him as an outstanding leader in this domain of medical research." The table of contents include the following plan of treatment — General Concepts, Definition of Constitution, Constitutional Anomaly and Constitutional Disease, Concept of Constitutional Strength and Weakness, Semiological Analysis of Constitution and Criteria for the Classification of the Individual Biotypes, Principal Ectotypes of General Constitution, Localized Constitutional

Anomalies and Inadequacies, Introduction, Constitutional Anomalies and Constitutional Inadequacies of the Skin and Cutaneous Appendages, Constitutional Inadequacies of the Skeleto-muscular System, Constitutional Anomalies of the Blood and the Hemolymphopoietic Organs, Constitutional Anomalies and Inadequacies of the Circulatory Apparatus, Constitutional Inadequacies of the Respiratory Apparatus, Constitutional Inadequacies of the Digestive Apparatus and Its Accessory Glands, Constitutional Anomalies and Inadequacies of the Urogenital Apparatus, Constitutional Anomalies and Inadequacies of the Nervous System, Constitutional Anomalies and Inadequacies of the Endocrine System, Principles of Therapy of Constitutional Inadequacies, Appendix to English Edition *Modern Analysis of Individual Human Biotype*. The style is excellent, clear, concise and readable with ease. The book is well printed, and convenient as to shape and size. We recommend this book to every medical student as indispensable to his intellectual armamentarium, and it should be in the hands of every practitioner of medicine who has any desire to be abreast of the medical conceptions of his times.

*Modern Medicine Its Theory and Practice*  
In Original Contributions by American and Foreign Authors. Edited by SIR WILLIAM OSLER, Bart, M.D., F.R.S., Late Regius Professor of Medicine in Oxford University, England. Third Edition, Thoroughly Revised. Re-edited by THOMAS MCCRAE, M.D., Assisted by ELMER H. FUNK, M.D., Professor of Medicine and Clinical Professor of Medicine, Respectively, in Jefferson Medical College, Philadelphia. General Index 126 pages. Lea and Febiger, Philadelphia, 1928. Price in cloth, \$1.00.

The General Index just published completes the third edition of the Osler-McCrae System of Modern Medicine. The publication of a General Index in this convenient form constitutes a great advantage, as it renders unnecessary the awkward handling of the separate heavy volumes, and saves much time in looking up the information.

tion concerning any desired subject treated in the System. The Index itself is logical, well itemed, and complete. It is indispensable to any owner of the System.

*Anatomical Studies on the Motion of the Heart and Blood.* The Tercentennial Edition of WILLIAM HARVEY'S *De Motu Cordis et Sanguinis in Animalibus*. A Facsimile Reproduction of the Original Edition of 1628, Together with a New Modernized English Translation, Conforming to the Original Condensed and Energetic Style. Translated and Annotated by CHAUNCEY D. LEAKE, Professor of Pharmacology in the University of California. Pages 154, Illustrated. Charles C. Thomas, Springfield, Illinois and Baltimore, Maryland, 1928. Price in cloth, \$3.50.

This is a very handsome volume set, printed and bound by The Collegiate Press, Menasha, Wisconsin. The cover design is by the Decorative Designers of Chatham, New Jersey. The front matter was designed and set by the Golden Hind Press of Madison, New Jersey. The facsimile of the Latin translation is reproduced by a new and exceedingly accurate process in photo-engraving. The type-face of the English translation is the beautiful Caslon Old Style No. 337, designed by William Caslon, an engraver of the early eighteenth century. Its characteristic is that of simple, honest design and perfect craftsmanship. The paper is 80 pound National Laid American Book, the binding is Holliston Book Cloth. All of these factors have resulted in a beautiful book, well printed and well-bound, and quite worthy of the epoch-making discovery the tercentennial of which it celebrates. The Contents consist of Part One, composed of the Facsimile of the Original (1628) Edition of Harvey's *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus*, Part Two, containing the English Translation and Annotations by Leake, the Translators Postscript, the Chronology of the Life and Harvey and the Index. The illustrations comprise the Portrait of Harvey at Fifty Years of Age, Janssen's Portrait of Har-

vey in the Royal College of Physicians of London, the Coat-of-Arms of the Harvey Memorial, Hempstead Church, Facsimile of Harvey's First Notation on the Circulation (1616), Experiments on a Bandaged Arm, Harvey Demonstrating the Heart to Charles I, two other Experiments on a Bandaged Arm, "The Most Pleasing Picture of Dr William Harvey", and "The Body of William Harvey Lapt in Lead." These illustrations add much to the interest and decorative value of this edition. The reproduction of the Latin text is very satisfactory and pleasing, Leake's translation is snappy and vigorous, expressing the original vigor of Harvey's writing. The annotations are all interesting. All in all this volume is a remarkably successful edition at relative low cost. The price puts it within the reach of every medical student, who should be encouraged to add this facsimile of one of the greatest classics in Medical History to their foundation libraries. We advise parents and friends who are thinking of Holiday or Birthday presents to medical students to consider this volume among the desiderata. Similarly to the physician who has not a first hand acquaintance with Harvey's great work we offer the advice that here is a handsome and quite inexpensive edition suitable to his requirements.

*The Opium Problem.* By CHARLES E. TERRY AND MILDRED PELLENS. For the Committee on Drug Addictions in Collaboration with The Bureau of Social Hygiene, Inc. New York, 1928.

This book is based on a report prepared for the Committee on Drug Addictions in collaboration with the Bureau of Social Hygiene, Inc., New York, by Charles E. Terry, M.D., and Mildred Pellens, the executive and assistant executive, respectively of the committee named. The committee was organized in 1921 and consists of Katharine Bement Davis, Ph.D., general secretary, Bureau of Social Hygiene, chairman, Stanley Cobb, M.D., professor of neuropathology, Medical School of Harvard University, Lafayette B. Mendel, Ph.D., Sc.D., professor of physiologic chem-

istry, Yale University, A N Richards, Ph D, Sc D, professor of pharmacology, University of Pennsylvania School of Medicine, Willard S Richardson, secretary, Laura Spelman Rockefeller Memorial, William F Snow, M D, general director, American Social Hygiene Association, and George B Wallace, M D, professor of pharmacology, New York University and Bellevue Hospital Medical College. This Committee was formed with a clear appreciation of a complex problem arising out of the chronic use of opium. It was decided that the first object to be sought in an intelligent approach was a determination of whether in opium addiction there existed a problem sufficiently important to warrant the institution of constructive efforts directed at solution. Certain questions suggested themselves as concerned with two main lines requiring investigation, i.e., chronic opium intoxication as a social problem and as an individual problem. It was attempted to answer satisfactorily the questions as to the extent, etiology, nature, and treatment of chronic opium intoxication, and how the problem concerned with this could best be solved. As a first step a thorough review of the literature was first taken up and completed. This volume presents a condensed report of the material covered in the above study, and in-

cludes the collective information concerning municipal, state, national and international control. The laws relating to opium in the United States, and the various citations in the literature on the Harrison Narcotic Law are given and criticized in Appendices. The bibliography contains 382 items. There is a very full index of the subject matter. The report is offered without dogmatic assertion, but with a full comprehension of the magnitude and great complexity of the problems involved. While the number of opium addicts in the United States could not be stated with accuracy, the Committee believes that the surveys indicate the existence of a very important social and medical problem. Because of the divergent views on the nature of chronic opium intoxication without sufficient scientific support the Committee accepts no one as satisfactory. The various laws and ordinances for the regulation of the opium traffic are discussed and their weakness or inadequacies pointed out. No very definite suggestions of improvement are offered beyond that of an adjustable policy toward chronic opium addicts, the members of the medical profession and those whose legitimate business brings them into contact with such addicts. A more intensive study of types of addicts and their physiologic and psychical reactions is advised.

# College News Notes

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## TENTATIVE PROGRAM ANNUAL CLINICAL SESSION

### The American College of Physicians

BOSTON, MASS

April 8-12, 1929

The Boston Committees will be as follows

#### *General Chairman*

J H Means

#### *Committee on Arrangements*

J H Means	Franklin White	J H Pratt
John H Musser	Henry A Christian	E P Joslin
John Phillips	G R Minot	Randall Clifford
C M Jones	W B Breed	C Wesselhoeft

#### *Committee on Clinics*

H A Christian	J H Pratt	C M Jones
G R Minot	E P Joslin	C Wesselhoeft

#### *Committee on Entertainment*

Randall Clifford	F B Talbot,	W B Breed
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#### *Committee on Hall*

Franklin White

The scientific sessions will be held in the Hotel Statler from two to four on Monday, Tuesday, Wednesday, Thursday and Friday afternoons, from eight to ten on Monday evening, and from eight to nine on Tuesday and Wednesday evenings. The following contributions have been received but their sequence has not yet been arranged

#### ADDRESS OF WELCOME

Dr A S Begg, Dean, Boston University School of Medicine  
Dr J M Birnie, President, Mass Medical Society  
Dr Lincoln Davis, President, Suffolk District Medical Society, Boston  
Dr D L Edsall, Dean, Harvard Medical School  
Dr A W Stearns, Dean, Tufts Medical School

#### REPLY

Dr C F Martin, Montreal, President of The American College of Physicians

## SYMPOSIUM ON DEFICIENCIES DISEASES

Dr G R. Minot—Fundamental Aspects of Deficiencies

Dr S B Wolbach—Pathology of Deficiencies

Dr Joseph Goldberger—Pellagra

Dr Randolph West—Pernicious Anemia

Dr Archibald H Beard, Minneapolis—Acute Yellow Atrophy

Dr G H Bigelow, Health Commissioner of Mass—The Health Officer and the Internist

Dr Harlow Brooks, New York City—Angina Pectoris

Dr L A Conner, New York City—Clinical Aspects of Trichiniasis

Dr C D Danzer, Brooklyn, N Y—Carotid Sinus Reflex (Hering), Its Use in the Diagnosis and Treatment of Certain Cardio-Vascular Diseases

Dr W W Herrick, New York City—Factors in the Prognosis of High Blood Pressure

Dr J B Murphy, New York City—Cancer

Dr L H Newburgh, Ann Arbor, Mich—Obesity

Dr L M Rabinowitch, Montreal—Diabetes in Children

Dr R J Reitzel, Galveston, Texas—Lead Poisoning from Snuff

Dr H C Solomon, Boston—Treatment of General Paresis

Dr Homer Swift, New York City—Rheumatic Fever

Dr A S Warthin, Ann Arbor—Syphilis of the Adrenal and its Relationship to the so-called Idiopathic Addison's Disease

Dr Benjamin White, Mass Department of Health—Critical Review of Sera and Vaccines in the Prophylaxis and Treatment of Disease (1 hour)

Dr J B Wolffe, Philadelphia—Motion Picture showing Electrocardiographic Interpretation of the Various Cardiac Arrhythmias

The following have agreed to present papers, but their titles have not been received yet

Dr C C Bass, New Orleans

Dr G C Hale, London, Ont

Dr George Blumer, New Haven

Dr J B Herrick, Chicago

Dr Lawrason Brown, Saranac Lake

Dr W L Holman, Toronto

Dr L F Baker, Baltimore

Dr E H Mason, Montreal

Dr R A Cooke, New York City

Dr J C Meakins, Montreal

Dr J W Crane, London, Ont

Dr W W Palmer, New York City

Dr C K Drinker, Boston

Dr J E Paullin, Atlanta

Dr A R Elliott, Chicago

Dr O H P Pepper, Philadelphia

Dr John Favill, Chicago

Dr M C Pincoffs, Baltimore

Dr David Riesman, Philadelphia

Clinics will take place from nine-thirty to twelve on Tuesday, Wednesday, Thursday and Friday mornings at the following hospitals

	<i>Capacity</i>
Beth Israel Hospital	200
Boston City Hospital	250
Boston City Hospital (South Dept)	16
Boston Dispensary	25
Children's Hospital	75
Homeopathic Hospital	8
New England Baptist Hospital	50
New England Deaconess Hospital	125
Massachusetts General Hospital	155
Peter Bent Brigham Hospital	225
Robert Breck Brigham Hospital	—

Preliminary programs for three of the hospitals are as follows

BOSTON CITY HOSPITAL  
*Surgical Amphitheater*

Hours	Tues Apr 9	Wed Apr 10	Thurs Apr 11
9 30-10	Dr J J Dowling Superintendent The Progress of the Boston City Hospital	Dr F W White Gastro-intestinal Cases	Dr E N Libby and Dr Thomas J O'Brien Cardiac Cases
10-10 30	Dr E A Locke Treatment of Pneumonia Demonstration of Cases	Dr W H Robey Cardiac Cases	Dr J M Faulkner Case Illustrating the Value of the Electrocardiogram Dr W G Lennox Epilepsy
10 30-11	Dr F W Palfrey Clinic of Unusual Cases	Dr W R Ohler Nephritis Cases	Dr J T Wearn Diseases of the Coronary Vessels Demonstration of Cases
11-11 30	Dr W B Castle Pernicious Anemia Demonstration of Cases	Dr E D Churchill Surgical Treatment of Pulmonary Tuberculosis Demonstration of Cases	Dr M Fremont-Smith Peptic Ulcer Demonstration of Cases
11 30-12	Dr G R Minot Treatment of Anemias Demonstration of Cases	Dr Soma Weiss Hypertension and Arteriosclerosis Demonstration of Cases	Dr Stanley Cobb Neurological Cases

*Boston City Hospital*

Hours	Friday, Apr 12	Thorndike Memorial Laboratory
9 30-10	Dr R. C Larrabee Cases of Disease of the Hemopoietic System	Demonstration of Researches concerning the following topics Wednesday and Thursday between 10 30 A M and 12 30 P M
10-10 30	Dr H Jackson, Jr Lymphoblastoma Demonstration of Cases	Dr Castle and associates—Anemia Dr Jackson and associates—Malignant Tumors
10 30-11	Dr G C Shattuck Tropical Diseases Demonstration of Cases	Dr Lawrence and Associates—The Physiology and Pathology of White Cells Dr Lennox—Epilepsy
11-11 30	Dr H W Dana Fluoroscopic Diagnosis in Chest Conditions Demonstration of Cases	Dr Minot and associates—The Blood Dr Nye and associates—Bacteriological Problems
11 30-12	Dr I J Walker Carcinoma of the Head of the Pancreas Demonstration of Cases	Dr Wearn and associates—The Capillaries Dr Weiss and associates—Vascular Problems

*Homeopathic Hospital*

Hours	Tuesday, Apr 9	Wednesday, Apr 10	Thursday, Apr 11	Friday Apr 12
9 30	Sterility Clinic Drs S R Meaker and A W Rowe Special emphasis to be placed on the constitutional fac- tors in sterility	Endocrine Clinic Dr C H Law- rence — Endocrine diagnosis and the- rapy Dr D W Drury— Endocrine disorders associated with oto- sclerosis and the Monierio syndrome. Dr W D Row- land—Eye findings in Endocrine Dis- orders Dr A W Rowe— Cases presenting outward evidence of Endocrine dis- turbance Dr L G Hoskins —Dementia Prae- cox Dr J C Janney— Follicular Hormone. Dr H Ulrich and Dr A W Rowe— Discussion on Sugar Metabolism as in- fluenced by insulin in pituitary disease	General Medical Clinic Dr W D Reid— Heart Clinic. Dr C W McClure — Intestinal Mi- graine Dr N H Garrick —Neurology Dr L R. Johnson —Lung Abscess, Diagnosis a n d Treatment, Bron- choscopy, the Use of the Broncho- scope in diagnosis and treatment	To be announced later

*Massachusetts General Hospital*

Hours	Tues Apr 9	Wed Apr 10	Thurs Apr 11	Fri Apr 12
9 30-10	Dr F T Lord— Thoracic Clinic	Dr W B Rob- bins— Demonstra- tion of Cases	Dr J B Ayer— Neurological Clin- ic	Dr G Blake— Demonstration of Cases
10-10 30	Dr W B Breed— Cases of Hyper- tension	Dr H Higgins and Dr F B Talbot— Pediatric Clinic	Dr W Herman— Psychotherapy of Gastro - intestinal Diseases	10-10 45 J H Means and Dr W O Thomp- son — Thyroid Clinic.



10 30-11	Dr H B Sprague —Cardiac Clinic	Dr R C Cabot and Dr Tracy B Mallory — Clinico- Pathological Con- ference	Dr. C M Jones— Gastro - intestinal Clinic	10 45-11 15 Dr F D Adams— Demonstration of Cases
11-11 30	Dr D L Sisco and Dr Walter Bauer —Endocrine Clinic	The above con- tinued	Dr A V Bock— Indications f o r Splenectomy	11 15-12 Dr F M Racke- mann — Anaphy- laxis Clinic.
11 30-12		Dr R R Wheeler —Diabetic Clinic	Dr W Richardson —Cases of Pernici- ous Anemia	

*Peter Bent Brigham Hospital*

Hours	Tues, Apr 9	Wed, Apr 10	Thurs, Apr 11	Fri, Apr 12
9 30-10	Dr L A Conner of New York Di- agnosis of certain forms of heart dis- ease	Dr J B Herrick of Chicago Car- diac disease — the result of infectious disease	Dr David Ries- man, Philadelphia, Mitral stenosis	Unassigned
10-10 30	Dr H A Chris- tian Chronic myo- cardial disease.	Dr Channing Frothingham Gallbladder dis- ease	Dr C L Derick Signs of persisting infection in acute rheumatic fever	Dr Reginald Fitz Vascular disease in diabetes mellitus
10 30-11	Dr E S Emery Results of treat- ment of duodenal ulcer	Dr Chandler Walker Bronchial asthma	Dr J P O'Hare Hemorrhagic ne- phritis	Dr S A Levine. Treatment of cer- tain types of car- diac arrhythmia
11-11 30	Dr W S Quinby Some considera- tions on the rela- tion of cardiorenal system to surgery of the urinary or- gans	Dr W P Murphy Anemia	Dr David Cheever A surgeon's views of the treatment of peptic ulcer	Dr Gilbert Hor- rax Treatment of trifacial neuralgia
11 30-12	Dr L G Richards Bronchoscopy in lung disease	Dr John Homans Thrombophlebitis	Dr Harvey Cush- ing Neurosurgical conditions	Dr H A Chris- tian Diuretics

## TECHNICAL EXHIBITS

Mr E. R. Loveland, Executive Secretary of The College, has completed all plans for the Technical Exhibits to be held in connection with the Clinical Session at Boston. An unusually fine arrangement for the exhibits is provided in the Ballroom Assembly of the Statler Hotel. Forty-four exhibit booths have been laid out, and practically every one has been contracted for by publishers of medical literature and manufacturers of equipment, pharmaceutical products, foods, etc. A special feature will be the exhibit of medical books and literature by the leading publishers of the country. These include

D Appleton & Company  
P Blakiston's Sons & Co  
F A Davis Company  
Paul B Hoeber, Inc  
Lea & Febiger

J B Lippincott Company  
The Macmillan Company  
The C V Mosby Company  
Thomas Nelson & Sons  
W B Saunders Company

Thus our members can examine all the new publications that have appeared not only during past recent years, but also during the present year.

No less important and interesting will be the exhibits of a large number of laboratory products companies, such as

G W Carnrick Co  
Deshell Laboratories, Inc  
Lavoris Chemical Company  
Merck and Company, Inc

The Wm S Merrell Company  
Richards, Inc  
Winthrop Chemical Company, Inc

There are in addition the exhibits of X-ray and physical therapy apparatus by such companies as Victor X-ray Corporation and the General X-ray Company, exhibits of Radiant Therapy by Britesun, Inc, exhibits of electrocardiographs and physiological instruments by the Cambridge Instrument Co, Inc, microscopes by Bausch & Lomb Optical Company, Luer Syringes and surgical and medical specialties by the MacGregor Instrument Company and the Cameron's Surgical Specialty Company, Helioglass by the Pittsburgh Plate Glass Company, infant feeding, food products, etc, by the Charles B Knox Gelatine Co, Inc, the Borden Sales Company, Inc, Kalak Water Company of New York, Inc, Horlick's Malted Milk Corporation, Merrell-Soule Company and the Battle Creek Food Company.

At the annual meeting of the Indiana State Medical Association in Gary, September 26-28, some rooms were set aside at the headquarters hotel as a meeting place for Fellows of The American College of Physicians. Dr Roscoe H Beeson, Fellow and Governor for Indiana, appeared on the program as a discussor at the symposium on diabetes. Dr Beeson was also elected Chairman of the Medical Section of the Indiana State Medical Association for the coming year.

Dr Samuel Ayres, Jr (Associate), Los Angeles, Calif, addressed the San Diego County Medical Society on September 11

on the subject, "Some Phases of Dermatology."

Dr Anton J Carlson (Fellow), Chicago, delivered on October 11 one of a series of public lectures at the Art Institute in Chicago under the auspices of the University of Chicago. This series of lectures was proposed by President Harper at the time the University was organized, and the subjects are on "Medicine through the Ages." Dr Carlson spoke on "Harvey."

Dr Frank Bethel Cross (Fellow), Brooklyn, N Y, has just recently returned from five weeks visit in Vienna. He com-

mends highly the splendid service rendered graduate students by the American Medical Association of Vienna, which has sole control of all recognized clinical courses given in English

Dr James G Carr (Fellow), Chicago, appeared on the program of the Third Annual All-Day Clinic of the Adams County Medical Society at Quincy, Illinois, on October 15

Dr Cyrus C Sturgis (Fellow), Ann Arbor, Michigan, addressed the Wayne County Medical Society October 2 on "Cardiac Disease"

Dr Carl V Vischer (Fellow), Philadelphia, is author of an article entitled "The Technic of Ultra-Violet Radiation in Pulmonary Tuberculosis," published in The Hahnemannian Monthly

Dr G Harlan Wells (Fellow), Philadelphia, addressed the Philadelphia County Medical Society at the September meeting on "Drugs as Antigens"

Dr Arthur C Morgan (Fellow) and Dr Orlando H Petty (Fellow), both of Philadelphia, addressed the Medical Society of Delaware at their meeting September 11-12 on the subjects "Treatment of Acute Cardiac Tragedies" and "Emergencies of Diabetes and How to Treat Them," respectively

Dr George E Pfahler (Fellow), Philadelphia, Professor of Radiology, will be in charge of the Louis J Kolb Foundation for the Treatment of Cancer. The fund of \$100,000.00, donated by Mr Louis J Kolb, of Germantown, shall be used for the purchase of a gram of radium and accessories for use in the treatment of cancer. The gift was made to the University of Pennsylvania Graduate School of Medicine, and will make possible the treatment with radium of the neediest patient with cancer

At the meeting of the Northwestern Ohio District Medical Society at Lima on October 9, the following Fellows of The College delivered addresses as shown

Dr Ralph Pemberton, Philadelphia, Pa., "Control of Arthritis and Rheumatism"

Dr Willard C Stoner, Cleveland, Ohio, "Diagnosis and Treatment of Syphilis with a Consideration of End-Results"

Dr Cyrus C Sturgis, Ann Arbor, Michigan, "Recent Advances in the Treatment of the Anemias"

Dr Charles W Stone, Cleveland, Ohio, "Early History of Organized Medicine in Ohio"

Dr Philip F Barbour (Fellow), Louisville, Ky, delivered an address on "Significance of the Leucocyte Count" at the banquet of the Southern Pediatric Seminar at Saluda on July 30

Dr Fritz B Talbot (Fellow), Boston, Mass, addressed the Pediatric Section of the Medical Society of the State of Pennsylvania at its meeting at Allentown, October 1-4, on "Endocrine Disturbances in Childhood"

Dr Charles W Stone (Fellow), Cleveland, Ohio, is President of the Ohio State Medical Association

Dr Daniel J McCarthy (Fellow), Philadelphia, Pa, addressed the Philadelphia Psychiatric Society at its symposium on legal medicine on October 12, on the subject "Responsibility"

Dr Daniel J McCarthy (Fellow), Philadelphia, Pa, spoke on "Medical Jurisprudence" before the Bucks County Medical Society at Buckingham, September 12.

About a year ago, Dr Lytle Motley (Fellow), Memphis, Tenn, severed his connection with the Baird-Brewer Hospital at Dyersburg, where he had been for twelve years, and moved to Memphis, where he has formed a partnership with Dr Conley H Sanford (Fellow). The practice of Doctors Motley and Sanford is being limited entirely to diagnosis and Internal Medicine, and their offices and laboratory are located in the Physicians & Surgeons Building

Dr Motley has been appointed to the Faculty of Medicine of the University of

Tennessee as Assistant in Medicine. He is also Attending Physician to the Memphis General Hospital and Associate Attending Physician to the Baptist Memorial Hospital.

Dr Sanford has recently returned from a five months' period of study at the University of Vienna, Austria.

At the recent meeting of the Seventh District Branch of the State Medical Society of New York, Dr Wardner D Ayer (Fellow), Syracuse, read a paper on "Early Diagnosis of Poliomyelitis," and Dr Carl J Wiggers (Fellow), Cleveland, gave a paper concerning his work on heart function, which is based on experimentation along a line somewhat different from that usually employed. Dr John Lichty (Fellow), Clifton Springs, a member of the Board of Regents of The College is Secretary of the Seventh District Branch.

Surgeon General Hugh S Cumming (Fellow), Washington, D C, was a speaker at a regional conference on Social Hygiene at Louisville, October 11-13, said conference being under the auspices of the State Board of Health and the local Social Hygiene Association.

Dr Lewellys F Barker (Fellow), Baltimore, Maryland, spoke on the topic "Headache" before the Medical Society of the County of Kings, New York City, October 19.

Dr Charles N Kavanaugh (Fellow), Lexington, Kentucky, delivered a paper on "Malta Fever" before the August meeting of the Cumberland Valley Medical Society, Dishman Springs, Kentucky.

Surgeon General Merritte W Ireland (Fellow), Washington, D C, on October 11 attended, at the Medical School of Harvard University, the dedication of a parapet of marble to the memory of four members of the Harvard Medical School unit who lost their lives in France during an air raid.

Dr George E. Pfahler (Fellow), Philadelphia, Pa, spoke before the Philadelphia

Roentgen Ray Society at its joint meeting with the Philadelphia County Medical Society on October 24 on "Results from Radiation Therapy in Malignant Disease."

Dr Benjamin W Black (Fellow), Oakland, Calif, formerly Medical Director of the Veterans Bureau, was recently appointed a member of the Medical Council of the U S Veterans Bureau.

Dr J C Lyter (Fellow), St Louis, Missouri, spoke on "Medical Aspects of Thyrotoxicosis" before the Macoupin County Medical Society at Carlinville, Illinois, on September 25.

Dr Lyter was guest of honor at a dinner given by Dr Charles E Trovillion, Superintendent of the State hospital, at Anna, Illinois, September 13.

Dr Charles C Conover (Associate), Kansas City, Missouri, addressed the Saline County Medical Society, Marshall, Missouri, September 12, on "The Human Heart in Infections."

Under the presidency of Dr William R. Bathurst (Fellow), Little Rock, Arkansas, the Southern Medical Association held its annual meeting at Asheville, North Carolina November 12-15.

Dr A J Carlson (Fellow), Chicago, Illinois, gave the first Harrington Lecture at the University of Buffalo on November 15-16, on the subject "Function of the Stomach in Health and Disease."

At the annual meeting of the Medical and Surgical Association of the Southwest, at Albuquerque, New Mexico, November 8-11, the following Fellows of The College appeared on the program:

Dr John H Musser, New Orleans, La., Internal Medicine, Dr Henry J Ullman, Santa Barbara, Calif, Radiology, Dr J A Myers, Minneapolis, Minn, Internal Medicine, Dr William Engelbach, St Louis, Mo, Endocrinology, Dr John W Shuman, Los Angeles, Calif, Bronchology.

Dr Wilburt C Davison (Fellow), Durham, North Carolina, and Dr James K Hall (Associate), Richmond, Virginia, were among the speakers at the Ninth District Medical Society meeting at Statesville, North Carolina September 27

Dr William C Chaney (Fellow), Memphis, Tennessee, gave an illustrated lecture before the Dyer County Medical Society, August 2, on "Diagnosis of Goiter"

Dr Seale Harris (Fellow), Birmingham, Alabama, spoke on "Role of Vitamins in the Etiology and Cure of Gastric and Duodenal Ulcers" before the Knox County Medical Society, Whittle Springs, Tennessee, August 7

At the All-Day Clinical Session of the same Society at Whittle Springs, on September 25, Dr James S McLester (Fellow), Birmingham, Alabama, appeared on the program, and Dr Ernest R Zemp (Fellow), Knoxville, Tennessee, had charge of the banquet

Dr Carl R Comstock (Fellow), Saratoga Springs, New York, addressed the Jefferson County Medical Society at Watertown, New York, September 13, on "Rôle of the Health Resort in Treatment of Cardiac Cases"

Dr James B McElroy (Fellow), Memphis, Tennessee, addressed the Montgomery County Medical Society at Dunbar Cave, Tennessee, August 16, on the subject "Hypertension"

Dr M L Turner (Fellow) and Mrs Turner, of Berwyn, Maryland, have just returned from a visit to Havana, where they attended the recent Convention of Spanish War Veterans. Dr Turner was Acting Assistant Surgeon in the Spanish American War Service in Cuba from 1898 to 1900, and thereafter was Major in the Sanitary Reserve Corps of the U S Army

Dr Aristides Agramonte, of Havana, who occupied a prominent place on the program of the last Clinical Session of The College at New Orleans, and who is an old college chum of Dr Turner, entertained Dr and Mrs Turner while in Havana. Dr Turner

reports that Dr Agramonte has been doing some work for the Rockefeller Foundation, in addition to his practice and college teaching at the University of Havana. Dr Agramonte has recently declined an offer from the Foundation that he go to the West Coast of Africa to study the Yellow Fever outbreak there. However, there have been over forty cases of Yellow Fever during the past summer in Brazil, and Dr Agramonte may lend his assistance there. He has recently been engaged in writing on "Ameloblastosis" and some other parasitic infections

Dr Stephen Cahana (Associate), Milwaukee, Wisconsin, is a member of the Wisconsin State Board of Health, term expiring February, 1934. He is also Chief of Staff of the Johnson Emergency Hospital, and since 1927 has been teaching Therapeutics and Prescription Writing at the Marquette Medical School

Dr Chas H Cocke (Fellow), Asheville, N C addressed the Tenth District Medical Society of North Carolina, on October 17th, 1928, at Burnsville, N C on the subject of "The Diagnosis of Early Clinical Tuberculosis, and on November 12th, gave a clinic before the Southern Medical Association at its meeting at Asheville, on the subject of "Massive Atelectasis of the Lung"

Dr E W Gehring (Fellow), Portland, Maine, was last spring made Chief of the Medical Service at the Maine General Hospital. We have authoritative reports that Dr Gehring and his assistants are doing excellent work in improving and expanding the service and standing of this department. Dr Gehring is the member of the Board of Governors representing the State of Maine.

Dr G Harlan Wells (Fellow), Philadelphia, Pa, is author of an article entitled, "The Treatment of Pernicious Anemia," in the October number of the Hahnemannian Monthly

† Henry I Klopp (Fellow), Superintendent of the Allentown State Hospital, Allentown, Pa, read the "Sixteenth Annual Report" of that institution before the Homeopathic Medical Society of the State of Pennsylvania on September 25, 1928

Several members of The College appeared on the program of the Seventh Annual Convention of the Eastern Homeopathic Medical Association held in Camden, New Jersey, October 20, November 1, 1928 They were

Dr Linn J Boyd (Fellow), New York City, "Diagnosis and Treatment of Epidemic Encephalitis"

Dr Donald R Ferguson (Associate), Philadelphia, Pa, "Massive Collapse of the Lung, Secondary to Bronchogenic Carcinoma"

Dr Carl V Vischer (Fellow), Philadelphia, Pa, "Management of the Chronic Tuberculosis Patient"

Dr G Harlan Wells (Fellow), Philadelphia, Pa, "The Present Status of the Treatment of Pneumonia by Serums and Antibodies"

Dr E Roland Snader, Jr (Fellow), Philadelphia, Pa, "A Modern Conception of the Treatment of Cardiovascular Syphilis"

Dr Harry M Eberhard (Associate), Philadelphia, Pa, "Causes of Failure in One Thousand Abdominal Operations"

Dr Wilburt C Davidson (Fellow), Dean of the Medical School of Duke University, Durham, North Carolina, addressed the Seventh District Medical Society of North Carolina at Lincolnton on October 8

Dr Drew W Luten (Fellow), St Louis, Missouri, spoke on "Congenital Syphilis" at a meeting of the Tenth Councilor District Medical Society of Arkansas on September 19

Dr Waller S Leathers (Fellow), Dean of the Vanderbilt University, School of Medicine, Nashville, Tennessee, was a speaker at the dedicatory services of the new College of Medicine and Hospital of the State University of Iowa on November 15

Dr George H Whipple (Fellow) of the University of Rochester, School of Medi-

cine, addressed the same gathering on November 17

Dr James H Hutton (Associate), Chicago, Illinois, spoke on "Ovarian Insufficiency" before the Rock Island County Medical Society of Illinois, October 16

Dr Otis B Nesbit (Fellow), Gary, Indiana, and Dr Charles H Neilson (Fellow), St Louis, Missouri, spoke before the Seventh District Medical Society at Martinsville, Indiana, October 30, on "Diphtheria and Scarlet Fever Prevention Work" and "Diagnosis of Sciatic Pain," respectively

Dr Thomas B Fitcher (Associate), Baltimore, Maryland, addressed the semiannual meeting of the Medical and Chirurgical Faculty of Maryland at Cambridge, Maryland, October 25-26, on "Diabetes Insipidus in Relation to Lesions of the Pituitary Gland and Hypothalamus"

Dr Edwin Henes, Jr (Fellow), Milwaukee, Wisconsin, was reelected Executive Secretary of the Interstate Postgraduate Medical Association of North America at Atlanta, October 19

Dr Morris H Kahn (Fellow), New York, N Y, addressed the Lackawanna County Medical Society at Scranton, Pa, November 13th on "Industrial Aspects of Heart Disease"

Lt Col Edward G Huber (Fellow), U S Army Medical Corps, was elected President of the honorary public health society, Delta Omega, at the Fifth Annual Meeting of that Society at Chicago, October 15

Dr Lewellys F Barker (Fellow), Baltimore, Maryland, was among those who conducted clinics at the clinical amphitheater of the University of Maryland, Baltimore, during November and December under the auspices of the Division of Medical Extension of that institution

Dr Howard T Karsner (Fellow), Professor of Pathology at the Western Reserve University, School of Medicine Cleveland Ohio, recently completed his duties as Chair

man of the Division of Medical Sciences of the National Research Council

Col Bailey K Ashford (Fellow), San Juan, Porto Rico, spoke on "Sprue and the Relation of Its Anemia to Pernicious Anemia" before the joint meeting of the Institute of Medicine of Chicago and Northwestern University Medical School, on November 15

Dr Aldo Castellani (Fellow), New Orleans, Louisiana is author of an article in the September issue of the American Journal of Tropical Medicine entitled, "Blastomycosis and Some Other Conditions Due to Yeastlike Fungi (Budding Fungi)"

Dr Paul P McCam (Fellow), Superintendent and Medical Director of the North

Carolina Sanatorium for the Treatment of Tuberculosis, Sanatorium, North Carolina, was recently elected President of the Southern Sanatorium Association

Dr Walter S Freeman (Fellow), Washington, D C., addressed the Philadelphia Neurological Society on October 26 on "Reflex Grasping and Gripping, its Significance in Cerebral Localization"

Dr Thomas G Simonton (Associate), Pittsburgh, Pa., was elected President of the Medical Society of the State of Pennsylvania at its 78th Annual Meeting at Allentown, Pa., October 3

Dr George E Holtzapple (Fellow), York, Pa., was elected one of the Vice-Presidents of the same organization

## SOUTHERN MEDICAL ASSOCIATION MEETING

at

Asheville, N C

November 12-15, 1928

The great extent to which Fellows and Associates of The College contributed to the program of the Southern Medical Association's meeting at Asheville is shown by the following report

Dr William R Bathurst (Fellow), Little Rock, Arkansas, presided over the entire Session as President of the Association

Dr J B McElroy (Fellow), Memphis, Tennessee, acted as Chairman of the Section on Medicine

Dr Lee Rice (Fellow), San Antonio, Texas, and Dr V P Sydenstricker (Fellow), Augusta, Georgia, acted as Vice-Chairman and Secretary respectively of the Section on Medicine.

Dr Edward C Mitchell (Associate), Memphis, Tennessee, acted as Chairman of the Section on Pediatrics

Dr J Russell Verbrycke, Jr (Fellow), Washington, D C., acted as Vice-Chairman of the Section on Gastro-enterology

Dr George B Adams (Fellow), Emory University, Georgia, acted as Chairman of the Section on Pathology

Dr W E Gardner (Fellow), Louisville, Kentucky, and Dr W R Houston (Fellow), Augusta, Georgia, were Chairman and Vice-Chairman respectively of the Section on Neurology and Psychiatry

Dr Earl D Crutchfield (Fellow), San Antonio, Texas, acted as Chairman of the Section on Dermatology and Syphilology

Dr Felix J Underwood (Fellow) of the State Board of Health of Jackson, Mississippi, was Chairman of the National Malaria Committee

Dr Stuart Graves (Fellow), Tuscaloosa, Alabama, Dr J H Musser (Fellow), New Orleans, Louisiana, and Robert Wilson (Fellow), Charleston, South Carolina, acted as Chairman, Vice-Chairman and Secretary respectively of the Section on Medical Education

Dr C N Kavanaugh (Fellow), Lexington, Kentucky, provided a scientific exhibit on Tularemia

Dr Earl D Crutchfield (Fellow), San Antonio, Texas, provided an exhibit, including photographs, of skin diseases

Dr F J Eichenlaub (Associate) and Dr Philip Matz (Fellow), Washington, D C, exhibited statistical studies bearing on diseases of the skin of ex-service men

Speakers and their titles of members of The College appearing on the program follow

Dr Charles L Minor (Fellow), Asheville,

"Indications for Thoracic Surgery in Tuberculosis"

Dr Charles H Cocke (Fellow), Asheville,

"Massive Atelectasis"

Dr Charles L Minor (Fellow), Asheville,

Address of Welcome in Behalf of the Buncombe County Medical Society and the Medical Profession of North Carolina

Dr Russell Verbrycke, Jr (Fellow), Washington, D C,

Response to the Address of Welcome in Behalf of the Southern Medical Association

Dr William R Bathurst (Fellow), Little Rock, Arkansas,

President's Address "The Promotion of the Common Welfare The Aim of Modern Medicine"

Dr Lee Rice (Fellow), San Antonio, Texas,

"Hypothyroidism"

Dr Sydney R Miller (Fellow), Baltimore, Maryland,

"Blood Stream Infections"

Dr Lea A Riely (Fellow), Oklahoma City, Oklahoma,

"Obesity and Hypertension"

Dr Seale Harris (Fellow), Birmingham, Alabama,

"Dieting the Ulcer Patient"

Dr J B McElroy (Fellow), Memphis, Tennessee,

"Is There a Disease Entity Known as Malignant Hypertension?"

Dr Ray M Balyeat (Fellow), Oklahoma City, Oklahoma,

"Perennial Hay Fever"

Dr J H Cannon (Fellow), Charleston, South Carolina,

"Arterio-Sclerotic Disease of the Kidney"

Dr George R Herrmann (Fellow), New Orleans, Louisiana, and Dr Robert Wilson (Fellow), Charleston, South Carolina, opened discussion on the above topic.

Dr W R Dancy (Fellow), Savannah, Georgia, and Dr Randolph Lyons (Fellow), New Orleans, Louisiana, opened discussion on "Hair Ball of the Stomach"

Dr W G Gamble (Associate), Charleston, South Carolina, opened discussion on "The Diagnostic Value of the Sugar Level in Pleural Fluids"

Dr C C Bass (Fellow), New Orleans, Louisiana, and Dr R S Leedingham (Fellow), Atlanta, Georgia, opened discussion on "Malaria Fever in the United States"

Dr Douglas Vander Hoof (Fellow), Richmond, Virginia, opened discussion on "Urinary Antiseptics"

Dr Allen H Bunce (Fellow), Atlanta, Georgia,

"A Clinical Consideration of Achlorhydria"

Dr E E Murphey (Fellow), Augusta, Georgia,

"Sodium Cacodylate in the Treatment of Pernicious Malaria"



Dr I B McIlroy (Fellow), Memphis, Tennessee, opened discussion on the above topic

Dr Newton S Stern (Fellow), Memphis, Tennessee,  
"The Clinical Recognition of the Arthritis"

Dr J I Paulin (Fellow), Atlanta, Georgia, and Dr Maurice C. Pincoffs (Fellow), Baltimore, Maryland, opened discussion on the above topic

Dr W R Houston (Fellow), Augusta, Georgia, opened discussion on "The Specific Action of Blood Transfusion in the Hemolytic Anemia of Pregnancy"

Dr C T Stone (Fellow), Galveston, Texas,  
"Massive Collapse of the Lung"

Dr J S McIester (Fellow), Birmingham, Alabama, and Dr Bryce W Fountaine (Fellow), Memphis, Tennessee, opened discussion on the above topic.

Dr Edward Clw Mitchell (Associate), Memphis, Tennessee,  
"Diarrheal Conditions as They Are Seen in the Southern States"

Dr W A Mulherin (Fellow), Augusta, Georgia, and Dr Wilburt C Davison (Fellow), Durham, North Carolina, opened discussion on "The Diagnosis of Child Tuberculosis"

Dr P P McCain (Fellow), Sanatorium, North Carolina,  
"A Report on the Study of Twenty-Five Thousand and Forty-Eight School Children for Tuberculosis, Organization of Clinics, Standards of Diagnosis Results"

Dr L R DeBuys (Fellow), New Orleans, Louisiana, opened discussion on the above topic

Dr J D Love (Fellow), Jacksonville, Florida, opened discussion on "Upper Respiratory Infections"

Dr Philip F Barbour (Fellow), Louisville, Kentucky, opened discussion on "Spinal Drainage in Infants and Children as a Diagnostic and Therapeutic Measure"

Dr W McKim Marriott (Fellow), St Louis, Missouri, opened discussion on "Pathogenesis and Treatment of Acidosis and Alkalosis"

Dr Wilburt C Davison (Fellow), Durham, North Carolina, opened discussion on "Acute Empyema in Infants Under Two Years of Age"

Dr Julius Friedenwald and Dr Theodore H Morrison (Fellows), Baltimore, Maryland,

"The Occurrence of Pyloric Obstruction Due to Some Unusual Causes"

Dr Seale Harris (Fellow), Birmingham, Alabama, and Dr Sidney K Simon (Fellow), New Orleans, Louisiana, opened discussion on the above topic

Dr Sidney K. Simon (Fellow), New Orleans, Louisiana,  
"The Medical Aspect of Chronic Duodenal Stagnation"

Dr W F Henderson (Fellow), New Orleans, Louisiana,  
"Dilated Duodenum, Roentgenologically Considered"

Dr William Gerry Morgan (Fellow), Washington, D C, opened discussion on Symposium on Chronic Duodenal Stagnation

Dr Joseph E Gichner (Associate), Baltimore, Maryland,  
"Mushroom Poisoning"

Dr Allan Eustis (Fellow), New Orleans, Louisiana, opened discussion on the above topic

Dr Martin E Rehfuess (Fellow), Philadelphia, Pennsylvania,  
"The Problem of Gastric Hyperacidity"

Dr F D Gorham (Fellow), St Louis, Missouri, and Dr Daniel N Silverman (Fellow), New Orleans, Louisiana, opened discussion on the above topic

Dr Seale Harris (Fellow), Birmingham, Alabama, and Dr George C Mizell (Fellow), Atlanta, Georgia, opened discussion on "The X-Ray and Clinical Diagnosis of Ulcers of the Stomach and Duodenum"

- Dr C S Danzer (Fellow), Brooklyn, New York,  
 "Fundamental Factors in the Pathogenesis and Treatment of Peptic Ulcer"
- Dr Julius Friedenwald (Fellow), Baltimore, Maryland, and Dr J E Knighton (Fellow), Shreveport, Louisiana, opened discussion on the above topic
- Dr J Russell Verbrycke, Jr (Fellow), Washington, D C,  
 "Causes of Gall Bladder Mortality"
- Dr H D Walcott (Fellow), Dallas, Texas,  
 "The Gall Bladder as a Cause of Chronic Urticaria Report of Cases"
- Dr John Witherspoon (Fellow), Nashville, Tennessee, and Dr G W F Rembert (Fellow), Jackson, Mississippi, opened discussion on "Causes of Gall Bladder Mortality" and also "The Gall Bladder as a Cause of Chronic Urticaria Report of Cases"
- Dr George B Adams (Fellow), Emory University, Georgia,  
 "The Life of John George Adams"
- Dr C W Duval (Fellow), New Orleans, Louisiana, and Dr Kenneth M Lynch (Fellow), Charleston, South Carolina, opened discussion on "Some Interesting Endothelial Reactions"
- Dr W G Gamble (Associate), St Louis, Missouri, opened discussion on "Sedimentation Rate of Erythrocytes," and also delivered a paper on "The Immediate Effects of Transfusion on Donor and Recipient"
- Dr W E Gardner (Fellow), Louisville, Kentucky,  
 "A Decade of Transition in American Psychiatry"
- Dr W R Houston (Fellow), Augusta, Georgia,  
 "Function in the Causation of Organic Disease"
- Dr Drew Luten (Fellow), St Louis, Missouri,  
 "Some Neurological Problems in Clinical Cardiology"
- Dr Ellsworth Smith (Fellow), St Louis, Missouri, opened discussion on the above topic
- Dr Beverly R Tucker (Fellow), Richmond, Virginia,  
 "Chorea—A Consideration of Its Various Forms"
- Dr H Mason Smith (Fellow), Tampa, Florida, opened discussion on the above topic.
- Dr M L Graves (Fellow), Houston, Texas,  
 "Unusual Complications in Acute Encephalitis with Illustrative Cases"
- Dr Titus H Harris (Fellow), Galveston, Texas, opened discussion on the above topic
- Dr A B Moore (Fellow), Rochester, Minnesota,  
 "Gastric Ulcer Its Signs, Location and General Roentgenologic Manifestations"
- Dr D N Silverman (Fellow), New Orleans, Louisiana,  
 "Recent Advances in Gall Bladder Physiology"
- Dr E S Lam (Fellow), Oklahoma City, Oklahoma,  
 "Drug Reactions"
- Dr F J Eichenlaub (Associate), Washington, D C,  
 "Demonstration of Cryocautery Method of Using Carbon Dioxide Snow"
- Dr Earl D Crutchfield (Fellow), San Antonio, Texas,  
 "Clinical Research in Dermatology"
- Dr C N Kavanaugh (Fellow), Lexington, Kentucky,  
 "The Epidemiology of Undulant Fever"
- Dr George W McCoy (Fellow), Washington, D C, opened discussion on the above topic
- Dr Felix J Underwood (Fellow), Jackson, Mississippi,  
 "The Control of Malaria as a Part of a Full time Health Department Program"

Dr William Krauss (Fellow), Memphis, Tennessee,

(1) "How to Make a Laboratory and Field Survey to Ascertain the Extent of Local Transmission,

(2) "Recent Experience with Plasmochin"

Dr Stuart Graves (Fellow), Tuscaloosa, Alabama,

"The Relation of Medical Education to the Public"

"What Constitutes a Desirable Medical Teacher?" was discussed from the following viewpoints

(a) "Viewpoint of a Full-Time Teacher" by Dr W McKim Marriott (Fellow), St Louis, Missouri

(b) "Viewpoint of a Clinical Teacher" by Dr Lewellys F Barker (Fellow), Baltimore, Maryland

(c) "Viewpoint of the Practitioner and the Public" by Dr James S McLester (Fellow), Birmingham, Alabama

"What Constitutes a Desirable Medical Student?" was also discussed from the following viewpoints

(a) "Viewpoints of a Pre-Clinical Teacher" by Dr William deB MacNider (Fellow), Chapel Hill, North Carolina.

(b) "Viewpoint of a Teacher of Pathology" by Dr Kenneth M Lynch (Fellow), Charleston, South Carolina

General discussion on the above topic was opened by Dr M L Graves (Fellow), Houston, Texas

Dr W Warner Watkins (Fellow), Phoenix, Arizona, as Secretary of the Medical and Surgical Association of the Southwest, arranged the annual meeting of that Society at Albuquerque, New Mexico, November 8-10

## OBITUARY

Dr Joseph Henry Byrne (Fellow), 167 West 76th Street, New York, N Y, died September 22nd of carcinoma of the stomach

Dr Byrne was born in 1862, and received his medical degree from Columbia University, College of Physicians and Surgeons in 1885. He was Visiting Physician to St Elizabeth's Hospital from 1912 to date, and to the Misericordia Hospital from 1924 to date. During the World War, he was Medical Examiner and member of the Local Draft Board No 125. Dr Byrne was a member of his County and State Medical Societies, a Fellow of the American Medical Association, a Fellow of the New York Academy of Medicine, and a member of the Association for the Study of Internal Secretions. He was also an alumnus of St Vincent's Hospital. He had been a Fellow of The College since 1915, having been one of the charter members at the time of its organization. He was elected Secretary of The College during 1917, and has held that position until February 24, 1921, when he was succeeded by Dr Frank Smithies, of Chicago, Illinois, as Secretary General.

## ANNALS OF CLINICAL MEDICINE

About two years ago, it became apparent to the Regents of The College that the interests of The College would be much better served if the official journal, then known as *Annals of Clinical Medicine*, were entirely under the control of The College and published directly by The College. It was thought that The College could more successfully promote circulation and advertising, expedite the appearance of the journal on a regular monthly schedule, simplify and minimize the difficulties of the editor and reduce the cost of printing and publication. Accordingly, the Board of Regents appointed a special Committee, consisting of Dr Alfred Stengel, Chairman, Dr George Morris Piersol, Dr Lewellys F Barker, Dr Clement R Jones and the Executive Secretary, Mr E R Loveland, to arrange a suitable plan for future publication and for termination of the contract with the Williams & Wilkins Company, of Baltimore, on June 30, 1927. Announcements of the plans of the Committee were made to members, and though the final details of the termination of the former publishing contract had not yet been fully consummated, The College began the publication of *Annals of Internal Medicine*, July 1, 1927, under a new volume series, I.

For the information of those who may be more especially interested in the matter, and particularly in view of a circular letter that has been addressed to former subscribers to the *Annals of Clinical Medicine*, it is appropriate to inform our membership regarding the steps that led to the discontinuance of former publication arrangements.

As the costs of recent volumes of *Annals of Clinical Medicine* were increasing at a rate which threatened embarrassing proportions in the future, while receipts from advertisements fell to negligible figures, it was thought best to terminate our relations with the publishers. Early negotiations failed to achieve this purpose because, though recognizing the indebtedness of The College for the printing of certain

extra pages in Volume V, and for certain deficits, the Regents failed to see how the publishers became entitled to an equity which they claimed in all future possible earnings of the *Annals* or how they were at any time involved in any "business hazard" when the College paid for all subscriptions and was expected to meet any deficits.

When agreement failed, suits were instituted by the publishers against The College in Baltimore and Wilmington, Del., but were withdrawn by them and the controversy settled by the payment of a sum of money covering the extra printing costs and the deficit, items which the Regents were quite prepared to pay for from the beginning.

During the publication of Volume I of the new journal, the Committee continued its work in securing an amicable settlement and termination of the former publishing contract. The stock of old numbers and volumes of *Annals of Clinical Medicine* has been placed in the storerooms of The College at Philadelphia. The old subscription lists have been secured, and all incompleting subscriptions received by the former publishers have been assumed and filled by The College.

Under the full control of The College, the circulation of *Annals of Internal Medicine* has been considerably increased, and a definite program of promoting advertising has been adopted. In every way, The College is seeking to improve the journal and to place the whole publication plan on a better basis.

The direct results already attained are (1) Entire freedom of The College in its publication policy, (2) Material reduction in the cost of printing and publication, (3) Greater convenience to the editor by having the journal printed at Ann Arbor, (4) Appearance of the journal on a definite schedule, 25th to 30th of each month, (5) Increase in circulation by about five hundred, (6) Material increase in amount and improvement in quality of advertising, (7) Abrogation of maximum page limit for reading matter.

## DEDUCTIBLE ITEMS FROM FEDERAL INCOME TAXES

By ruling of the U S Commissioner of Internal Revenue, The American College of Physicians has been approved for exemption from income tax, and all amounts (*Initiation Fees, Life Membership Fees and Dues*) contributed to The College shall be deductible from the gross income of such donors when filing Income Tax Returns

Also traveling expenses of physicians incurred in attendance at meetings of medical associations are deductible from Federal Income Taxes The Board of Tax Appeals made this decision October 2, 1928, in passing upon the appeal of Dr Cecil M Jack (Fellow), Decatur, Illinois "The decision becomes final at the expiration of six months from its promulgation, unless an appeal is taken to the courts before that time The Commissioner did not appeal, however, when the Board of Tax Appeals rendered final decisions in favor of ministers and of chemists, in cases identical in every essential circumstance with the present case. In those decisions, the Commissioner officially acquiesced, without waiting for six months to expire, and there seems to be no reason why he should follow a different course now"

It is believed that since the Commissioner of Internal Revenue first denied to physicians the right to deduct traveling ex-

penses in 1922, the medical profession has paid a large sum into the treasury and that now, subject to certain limitations of time within which claims for refunds may be filed, the refund of all of this money may be applied for by these physicians Applications for refunds may be filed at once For the tax years 1924 and 1925, claims for refunds must be filed within four years from date of payment For the tax years 1926 and 1927, three years are allowed, and for the tax year 1928, two years are allowed Applications must be filed on special forms provided for the purpose These forms can be secured from the local collector of internal revenue Separate applications for each year must be made, and must be filed with the collector of internal revenue within whose district the refundable money was paid Each applicant must specify that his appeal is based on the decision of the Board of Tax Appeals in *Jack v Commissioner of Internal Revenue*

## CORRECTION

Dr Reynold Webb Wilcox (Fellow) appears in the 1927-28 YEAR BOOK under "Madison, Connecticut" Dr Wilcox's listing should have been "90 Bayard Lane, Princeton, New Jersey," where he has made his home for several years

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(Formerly official journal of The American College  
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# The Hemopoietic Effect of Nuclear Extractives in Human Anemias\*

By N W JONES, M D, B I PHILLIPS, M D, OLOF LARSELL, Ph D, and  
H T NOKES, M D, Portland, Oregon

*(From the Departments of Anatomy and Medicine, University of Oregon  
Medical School)*

WITH no more than passing reference (1, 2, 3, 4) to the experimental work upon which the following clinical studies have been founded, we wish in this paper to relate briefly observations we have made on the effect of nuclear extractives in the treatment of anemia in human patients. The nuclear extractives used, as reported elsewhere, have been obtained by the methods of Hammarsten and of Kossel-Neumann from various organ sources, and have been considered to be nucleo-proteins and the sodium salts of nucleic acids. An unknown hemopoietic stimulant exists in both of these nuclear extractives, and because from both experimental and clinical suggestive evidence we have thought a greater effect upon blood regeneration was seen from the use of both extractives in combination than from the use of either one alone, we have administered to anemic patients capsules containing one-fourth gram of each extractive. In the earlier part of the clinical work we employed the intravenous injection of from one-fourth to one gram of the sodium salts

of nucleic acids obtained from the washed nuclei of the blood cells of the fowl. There was observed, however, in about one-half of the patients so treated, a serum-like reaction of sufficient degree to make this method objectionable. In consequence, oral administration of the extractives was adopted with seemingly the same effect upon the blood picture.

In the entire study thus far made we have obtained nuclear extractives from eight different organs, and the percentages of extractives obtained per given weight of organ substance has been as follows: chicken corpuscles about 3 per cent, beef spleen 2.4 per cent, beef liver 1.8 per cent, beef kidney 0.9 per cent, beef heart muscle 0.5 per cent, salmon liver 2.4 per cent, beef thymus per cent and beef pancreas per cent not determined. All of the above extractives, with the exception of those obtained from beef heart muscle, have been used in the produced anemia of experimental animals. The animals have shown the same type of response in reticulated cells, hemoglobin content and in red blood cell counts that has been seen in anemic animals and in human patients with pernicious anemia to whom a high

\*Aided by grant No. 128 from the Committee on Medical Research of the American Medical Association.



liver diet has been administered. The hemopoietic stimulation observed, however, has seemingly shown a more definite relation to the quantity of extractives administered than to the organ from which they were obtained. The best results followed the administration of extractives from chicken corpuscles and the next most marked results from the use of extractives from beef spleen and from salmon liver. Both of the latter extractives gave better responses than did those from beef liver. For an as yet unknown reason the extractives from thymus have given the least response of all. In the anemias of human patients we have employed thus far the extractives obtained from chicken blood cells, beef liver and beef spleen, and we have seen in these patients, for the most part, similar effects upon the blood production.

#### NUCLEAR EXTRACTIVES OBTAINED FROM THE WASHED NUCLEI OF CHICKEN BLOOD CELLS

It was found experimentally that the hemopoietic stimulant existed only in the nucleus of the chicken blood cell. The cytoplasm of the cell alone—and consequently the hemoglobin element of the cell—possessed no power to stimulate blood formation in the animal body. It was from the washed nuclei of the blood cells, therefore, that we obtained the first nuclear extractives used in this series of studies.

Tables I and II, respectively, give, briefly, the important data in a series of pernicious anemia patients and in a series of patients having secondary anemias. A temporary slight rise in

hemoglobin and in the red cell count was observed in most of them.

Patient No. 1, table I, suffered a severe reaction from the intravenous administration of the extractives, and his blood counts showed no temporary rise in hemoglobin and red cells, as the blood of the other two patients did show. This patient had had a splenectomy done some months before. We have seen the same response from the intravenous injection of similar nuclear extractives in splenectomized rabbits. The third patient showed no more effect from the long continued use of liver than she had temporarily shown in response to the injection of 0.5 gm sodium nucleate.

In a similar way the patients having chronic secondary anemias showed usually a temporary rise in hemoglobin and red cell content in response to one administration of sodium nucleate. In patient No. 2, bleeding uterine fibroids seemingly prevented any rise, and there was also no effect upon the blood seen from the use of liver. In patient No. 5 a temporary rise in blood count was seen to follow each of two injections of 0.25 gm doses.

The effect of the oral administration of nuclear extractives obtained from whole chicken blood and the effect of the oral administration of the washed nuclei themselves is now being studied and a report of these observations will be made later.

#### NUCLEAR EXTRACTIVES OBTAINED FROM BEEF LIVER

A larger number of patients with anemia have been treated clinically by us with the nuclear extractives ob-

SODIUM NUCLEATE FROM WASHED NUCLEI OF CHICKEN BLOOD CELLS  
CASES OF PRIMARY ANEMIA

TABLE I

No	Date	Name	Age	Sex	Diagnosis	Hb %	RBC	Retic %	VI	Therapy	Duration of Anemia Remarks
1	10-27-26	AEWP	68	M	Pernicious	58	223		145	1 gm	2-3 years
	10-29-26				Anemia	49	195			Intravenously	Severe reaction lasting three days
	11-16-26					57	225				Patient continued on liver diet without change in blood picture until his death 4-20-27
	1-13-27					40	161				Had previously had a splenectomy and a cholecystectomy
2	11-5-26	MHC	73	F	Pernicious	72	285		129	0.5 gm	1 year
	12-1-26				Anemia	87	367			Intravenously	Chill and fever
3	11-3-26	AE	62	F	Pernicious	86	382		115	0.5 gm	3 years
	11-19-26				Anemia	96	422		114	Intravenously	Chill and fever Continued on liver diet until death on 9-8-27

SODIUM NUCLEATE FROM WASHED NUCLEI OF CHICKEN BLOOD CELLS  
CASES OF SECONDARY ANEMIA  
TABLE II

No	Date	Name	Age	Sex	Diagnosis	Hb %	RBC	Retic %	VI	Therapy	Duration of Anemia Remarks
1	11-6-26	BT	39	F	Chr Chole- cystitis	69	441			0.5 gm	3 years
	12-3-26					80	467			Intravenously	No reaction
	12-30-26					65	439				
2	11-23-26	CBW	39	F	Bleeding	64	421			0.75 gm	3 years
	11-29-26				Uterine Fibroids	57	448			Intravenously	Chill, fever, vomiting Liver feeding also gave no effect
3	12-31-26	MM	32	F	Chr Chole- cystitis	85	436			0.5 gm	4½ years
	1-5-27					94	444			Intravenously	No reactions
4	12-21-26	RGL	54	F	Chr Chole- cystitis	36	203		1.05	0.5 gm	6 months
	12-21-26					38	212			Intravenously	Chill, fever, headache
	12-22-26					35	201				Liver feeding also gave no effect
	1-5-27					27	134				Death
5	10-18-26	JP	62	F	Chr Chole- cystitis	81	335			0.25 gm	6 months
	10-29-26					78	417			Intravenously	No reaction
	11-10-26					73	328			0.25 gm	Chill for ½ hr
	12-16-26					78	382			Intravenously	
	12-29-26					75	325				
6	1-20-27	BM	70	F	Chr Chole- cystitis	81	429			0.5 gm	4-5 years
	1-28-27					89	442			Intravenously	No reaction
	2-7-27					83	321				
7	11-8-26	HHN	40	F	Chr Chole- cystitis	79	480			0.25 gm	3 years
	3-17-27					88	485			Intravenously	No reaction Cholecystectomy 6-21-26

tained from other sources than chicken blood cells, and especially from beef liver, because of the greater ease of manufacturing them in quantity and also because of the present interest in the liver treatment of pernicious anemia (See tables III and IV, and graphs 1, 2, and 3) We have been able in several instances to run like cases as rough clinical controls We have also on several occasions treated a given patient with nuclear extractives from liver, from spleen and by liver feeding for stated periods of time to compare if possible the relative stimulant effect of the different substances In the main, both in the case of primary anemia and in that of secondary anemia like effects have been noted Our study of pernicious anemia patients during the past year has shown a variation in individual response seemingly due to the fact that a number of the patients had been eating liver before coming to us In these patients the rise in the reticulated cells has been modified or absent Case 6, table III, illustrates this point well Case 7 indicates the necessity of using sufficiently large doses of the extractives

Patients with secondary anemias showed a less uniform response to the administration of nuclear extractives, and to liver feeding, than did patients suffering from pernicious anemia However, those patients who had suffered an acute anemia from hemorrhage, from an acute and transitory infection, or even in certain instances in which the cause has not been recognized, have shown quite as dramatic a response to treatment as any

person with pernicious anemia Compare, for example, in table IV, cases Nos 5, 6, 7, 8, 9, 10, 11, 12, 14, 15 and 16 Rough clinical controls have been run as of cases Nos 10-A, 13-A, 14-A, 15-A, and 16-A The identical twins, Nos 13 and 13-A were under observation and control very unsatisfactorily but an obvious improvement was noted in the treated patient over the progress of the untreated one The anemia of chronic cholecystitis did not seemingly respond much until after the gallbladder was removed Then, however, the patient treated with nuclear extractives, or with liver feeding, seemingly regained a normal blood content and a clinical recovery more rapidly than the patient not so treated The same statement may be made in regard to patients with anemia due to uterine fibroids, hyperplastic sinusitis, etc This point is stressed because there is now a widespread suspicion that the use of liver or its extractives holds a certain specificity for pernicious anemia and that persons suffering from secondary anemias are unimproved by their use This suspicion is wholly at variance with our experience Surely, case No 6 belies this assumption, for the child had been treated for months with dietetic and medicinal measures without effect and the use of 3 gm daily of nuclear extractives for a period of seven weeks produced quite as noteworthy a response in blood content and clinical recovery as could be seen in pernicious anemia We have been of the opinion that the probable cause of failure to gain on the part of some persons with secondary anemia lies in the relative balance be-

SODIUM NUCLEATE AND NUCLEOPROTEIN FROM LIVER  
CASES OF PRIMARY ANEMIA

TABLE III

No	Date	Name	Age	Sex	Diagnosis	Hb %	RBC	Retic %	VI	Therapy	Duration of Anemia Remarks
1	11-28-27	JE	80	M	Pernicious Anemia	35	115			450 cc whole blood	44 years Left hospital feeling well
	12-10-27					35	226			450 cc whole blood	
	12-15-27					43	226			1 gm tid increased	
	1-9-28					72	368			to 2 gm tid in one	
	3-22-28					83	379			week	
2	2-8-28	WL	62	M	Pernicious Anemia	41	173	13	123	2 gm tid	Second relapse of anemia Graph No 1 Left hospital feeling well
	2-15-28					43	208	80			
	2-22-28					73	316	240			
	2-24-28					104	512	20			
3	1-29-28	EC		M	Pernicious Anemia	38	126			1 gm tid	
	1-26-28					43	143			2 gm tid	
	1-30-28					50	204			3 gm tid	
	2-28-28					90	436				
	3-26-28					90	440				
4	2-2-28	OP		M	Pernicious Anemia	28	103			High protein diet—	Continues to feel well
	2-23-28					25	097			profoundly ill	
	2-27-28					28	102			Iron citrate	
	3-12-28					57	228			4 gm. tid—started	
	3-26-29					80	319			6 gm tid	

Marked clinical improvement

TABLE III, Continued

5	4-13-27 4-15-27 4-18-27	KAD	79	F	Pernicious Anemia	56 62 70	2 14 2 30 2 07	1 33	2 gm tid	Acute relapse for 2 wks Death—with rising hemo- globin
6	3-14-28 3-21-28 3-30-28 4-13-28 4-28-28	E.L.P	42		Hyperplastic Sinusitis Dental sepsis Pern Anemia?	114 93 87 81 90	4 50 4 43 4 17 4 21 4 10	0 1  1 14 0 3 6 1 14	Previous liver feeding and liver extracts Off liver 1 week Off liver 2 weeks 3 gm tid	Weakness, dizziness and anemia, since Nov 1927 Radical antrum op Dental extraction Marked clinical improve- ment
7	9-10-27 9-20-27 10- 1-27 10-10-27 10-29-27 11-12-27 11-25-27 12-20-27	L.H.S		M	Pernicious Anemia Diabetes	42 41 61 66 83 90 91 100	1 47 1 32 1 88 2 35 3 25 3 58 4 17 3 82		1 gm tid 1 5 gm tid  2 gm tid	Marked clinical improve- ment

SODIUM NUCLEATE AND NUCLEOPROTEIN FROM LIVER  
CASES OF SECONDARY ANEMIA

TABLE IV

No	Date	Name	Age	Sex	Diagnosis	Hb %	RBC	Retic %	VI	Therapy	Duration of Anemia Remarks
1	4-2-27 4-10-27	JK	69	F	Chr Chole- cystitis	76 91	4.12 4.66			1 gm tid	1 year
2	4-4-27 4-11-27	GC	45	F	Uterine Hemorrhage	84 88	4.65 4.73			1 gm tid	3½ years
3	3-25-27 4-7-27	AJL	38	F	Chr Chole- cystitis	75 84	4.40 4.62			0.5 gm. tid	3 years
4	3-15-27 3-17-27 4-1-27 4-9-27	GLS	50	F	Uterine Fibroid	59 61 73 65	3.89 3.98 4.66 4.26			0.5 gm. tid 1.0 gm tid	6 months Hysterectomy 4-11-27
5	4-13-27 6-9-27	JC	15	M	Upper Resp Infection	52 95	5.01 6.12			0.5 gm tid	3-4 months Graph No 3 Health rapidly regained Failure of previous therapy
6	12-31-26 2-20-27 1-8-27	BP	2	M	Malnutrition Upper Resp Infection	38 98 100	3.40 5.68 5.86			1 gm tid 1 gm stopped	6 months Health rapidly regained Failure of previous therapy
7	1-26-27 5-21-27 6-1-27	BP	13	F	Unknown Cause	72 96 90	3.92 5.74 5.25			1 gm tid	1 year Severe menstrual flow

TABLE IV, Continued

8	5-19-27 6-9-27	W	24	F	Unknown Cause	57 92	395 524	0.6 gm tid	2-3 years, periodically
9	7-18-27 7-25-27 8-20-27 8-22-27 9-10-27	LR	26	F	Hemorrhage Peptic Ulcer	20 38 74 58 94	141 264 442 360 524	550 cc whole blood 1 gm tid	Acute onset  Gastroenterostomy  Discharged
10	8-3-27 8-29-27 9-13-27	IW	19	F	Hemorrhage Abortion	32 64 95	195 340 524	2 gm tid	Acute onset  Discharged
10-A	8-30-27 9-30-27 10-8-27	Mrs D	28	F	Hemorrhage Abortion	51 64 68	298 389 400	Curettement	Acute onset Used as control Discharged
11	2-22-28 3-6-28 3-20-28 4-2-28	CB	47	M	Lobar Pneumonia	111 48 60 86	528 352 408 608	2 gm tid	Anemia following lobar pneumonia Graph No 2  Discharged
12	8-7-27 8-17-27	I.Z	45	M	Cellulitis of Thigh	48 95	302 514	2 gm tid	Anemia following cellulitis Discharged



TABLE IV, Continued

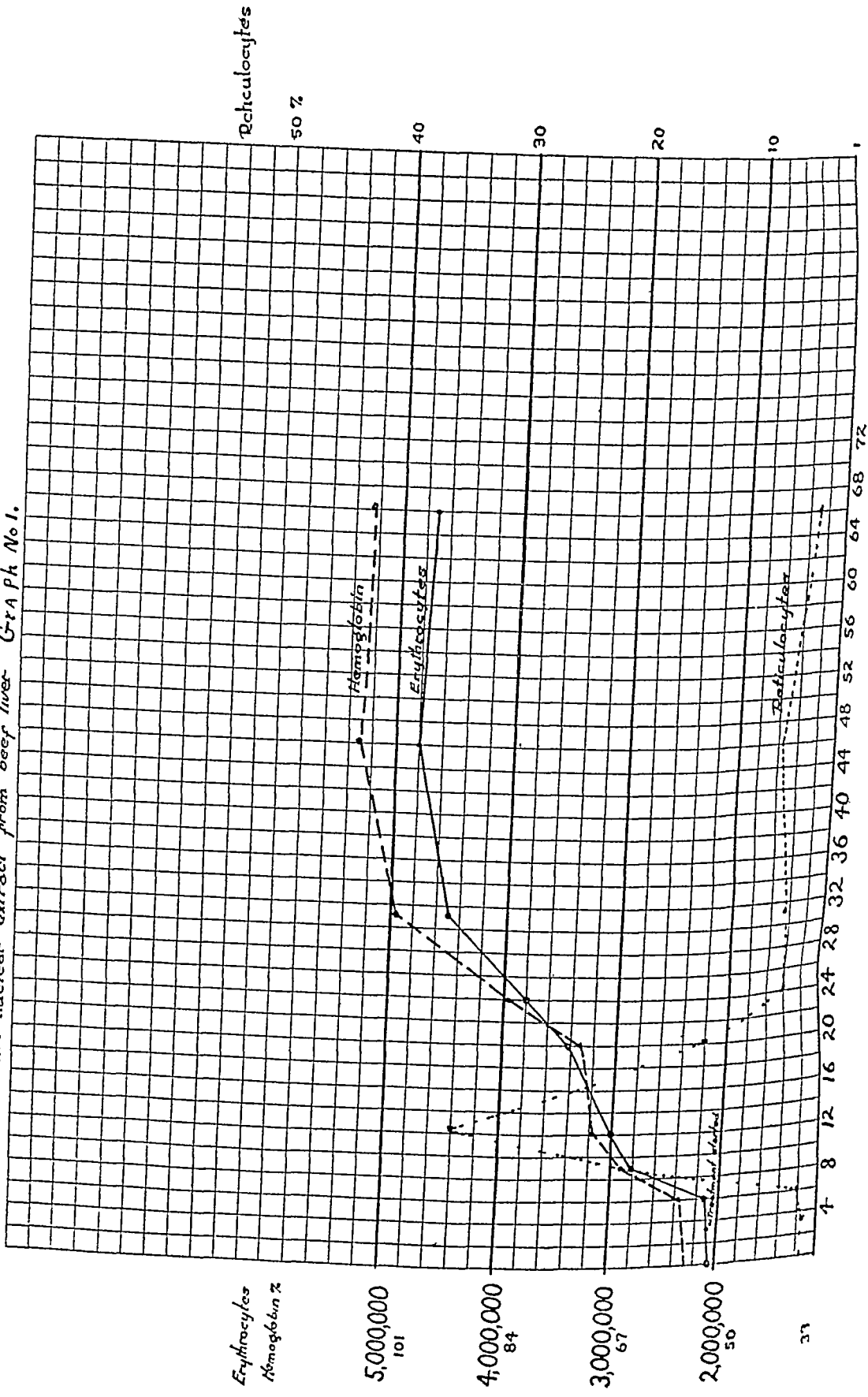
I3	10-12-27 11-14-27 1-11-28	Martha	I	F	Nutritional Disturbance	38 50 55	296 420 480	1 gm tid	Identical twins
I3-A	10-12-27 11-14-27 1-11-28	Mary	I	F	Nutritional Disturbance	38 40 40	319 380 470	Dietetic tr only	Used as a control
I4	12- 9-27 12-15-27 12-20-27 1-11-28 1-17-28	FA	22	M	Hemorrhage Peptic Ulcer	19 30 50 75 89	128 230 322 498 524	500 cc whole blood 2 gm tid	Acute onset Marked clinical improve- ment
I4-A	12-20-27 12-23-27 1-11-28 1-17-28	CB	32	M	Pulmonary Hemorrhage Cause Unknown	40 36 40 46	252 262 303 324		Acute onset Case used as a control
I5	8- 7-27 8-10-27 8-17-27	LZ	21	F	Following Acute Peri- tonitis	52 84 96	302 437 514	2 gm tid	Slow recovery Acute onset
I5-A	8-26-27 8-28-27 8-31-27	LH	19	F	Acute Hemorrhage, Abortion	30 40 58	192 210 250	Transfused whole blood	Rapid recovery Acute onset Used as control Slower recovery

TABLE IV, Continued

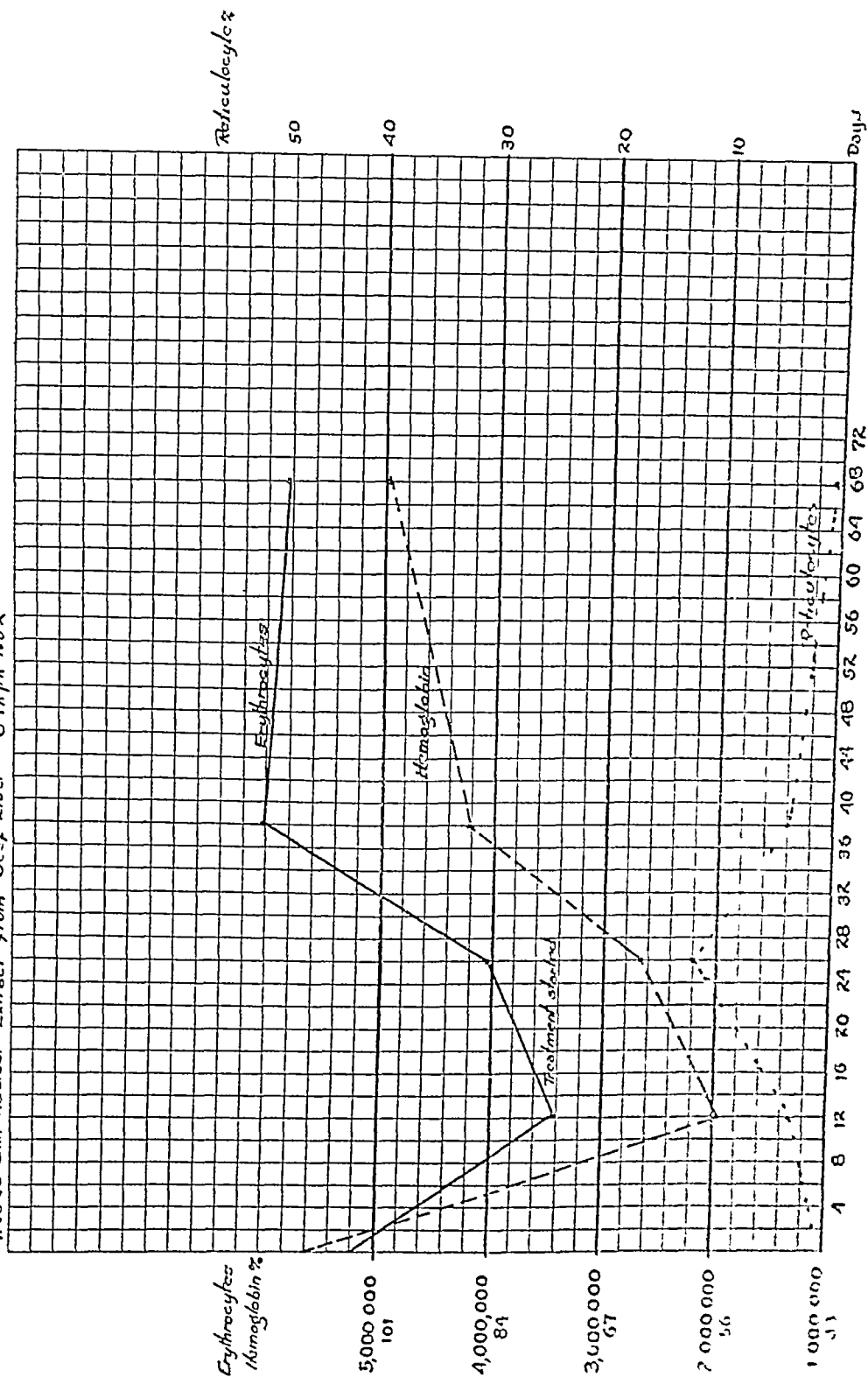
16	11-8-27	FLW	48	F	Hyperplastic Sinusitis	73	4.15		Anemia several years
	11-15-27								Radical antrum operation
	11-30-27					52	3.75	2 gm tid	Secondary hemorrhage
	12 5-27					47	2.87		Liver ext stopped
	12-21-27					69	4.05	liver 1 lb	Discharged—good recovery
	1-7-28					89	4.65		
16-A	3-20-28	AM	23	F	Purulent Sinusitis	60	4.02	Intra-nasal puncture	Acute secondary hemorrhage
	4-20-28					54	4.52		Used as control
	5-24-28					72	5.10		Slow recovery
17	3-17-28	CZ	63	F	Carcinoma Stomach	48	3.74	2 gm tid for 12 days	Discharged
	4-23-28					44	3.54		
	1-30-28					60	4.24	3 gm tid for 19 days	
	5 12-28					76	4.68	Partial gastrectomy	
18	10-6-27	AN	25	F	Sickle cell (?)	62	3.75	1 gm tid	Anemia for at least 10 yrs
	11-12-27					71	4.02		Graph No 3
	12-12-27					76	4.35		Severe menorrhagia
	1-6-28					79	4.48		
	2 22-28					68	3.50		
	3 22-28					80	4.56		Very fair clinical improvement

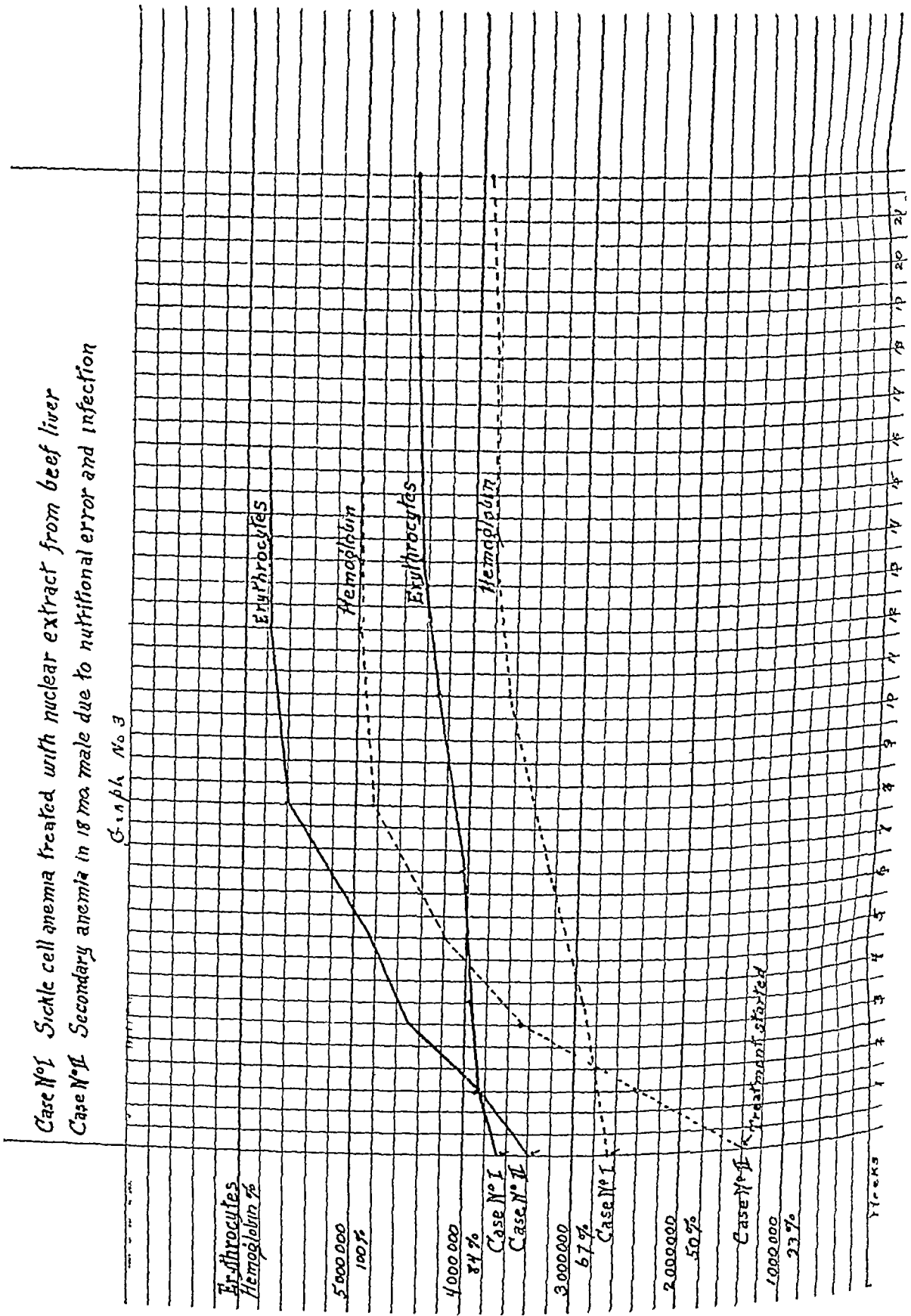
W L - Male Age 62 - Pernicious Anemia

Treated with nuclear extract from beef liver - Graph No 1.



C.B. Male, age 47 Anemia following lobar pneumonia  
Treated with Nuclear Extract from Beef Liver Graph No. 2





tween the cause of the anemia operating and the capacity of the hemopoietic centers of the bone marrow to respond to stimulation. Case No 17, a woman with carcinoma of the stomach, made no gain on 6 gm nuclear extractives daily in 12 days, but after partial gastrectomy, showed a gain of 32% hemoglobin and 114 million red cells on 9 gm of the same extractives in 19 days. The control cases 10-A, 14-A, 15-A and 16-A might suggest that the patient would not have shown this gain had she not been so treated.

Case No 18, a young white woman suffering from a chronic anemia which simulated sickle cell anemia (to be reported by Drs Hunter and Adams from the Department of Pathology, University of Oregon) showed marked clinical improvement under the administration of 1 gm liver extractives three times daily. Gastrointestinal distress disappeared, the pallor of her skin and mucous membranes became much less marked and the hemoglobin and red cell content progressively increased, over a period of five months, from 62 to 80 per cent and 3.75 million to 4.56 million respectively. Under no other form of treatment had improvement ever been observed.

#### NUCLEAR EXTRACTIVES OBTAINED FROM BEEF SPLEEN

Six patients suffering from pernicious anemia have been treated by the use of sodium nucleates and nucleoproteins obtained from beef spleen. A resume of their data is given in table V. Graph No 4 illustrates the progress under treatment of patient No 1. Two patients present the

same initial rise in reticulocyte count, the rapid gain in hemoglobin and red blood cell content, and the same clinical improvement observed from high liver feeding. Patients No 2 and 3 had previously eaten liver, and the increase of the reticulated cells was delayed and less high than in patients Nos 1 and 4 who had not eaten liver. Patient No 2 was given spleen extractives, 9 gm for 4 days and 12 gm for 14 days, with a rise of 15% hemoglobin, then liver extractives 9 gm for 15 days, with a rise of 22% hemoglobin, then spleen extractives 9 gm for 9 days with a rise of 5% hemoglobin, at which time she returned home on liver feeding. Patient No 3 was given 9 gm spleen extractives for 14 days and showed a gain of 14% hemoglobin, then 9 gm liver extractives for 4 days with a gain of 5% hemoglobin, then for 10 days, 9 ounces of raw liver was given with a gain of 4% hemoglobin, and finally for a period of 21 days 3 vials of Lilly's liver extract were added to the 9 ounces of raw liver with a gain of 5% hemoglobin. The numbness and tingling of the hands and feet, from which this patient suffered, did not disappear. We have seen the paresthesia disappear twice in pernicious anemia patients, once from liver feeding and once from the use of the nuclear extractives obtained from spleen. For the most part, however, we have seen no effect upon the symptoms of cord lesions.

*Discussion* In presenting at this time this brief report of our clinical observations on the use of nuclear extractives obtained from different ani-

SODIUM NUCLEATE AND NUCLEOPROTEIN FROM SPLEEN  
CASES OF PRIMARY ANEMIA

TABLE V

No	Date	Name	Age	Sex	Diagnosis	Hb %	RBC	Retic %	VI	Therapy	Duration of Anemia Remarks
1	3-14-28	NMCC	58	M	Pernicious Anemia	56	216	14	118	3 gm tid	Duration 3 years Graph No 1
	3-17-28					66	280	20			
	3-20-28					70	300	34			
	3-28-28					75	341	12			
	4-4-28					83	380	4			
	4-11-28					100	450	45			
2	3-29-28	KMCC	70	F	Pernicious Anemia	47	180	01	134	3 gm tid	Duration 5 years Had previously eaten liver Marked clinical improvement
	4-2-28					55	194	20		4 gm tid	
	4-9-28					54	196	66			
	4-16-28					62	218	110		3 gm tid liver ext. (replaced spleen)	
	4-27-28					79	320	60		3 gm tid spleen ext (replaced liver)	
	5-1-28					84	314	40			
	5-9-28					89	315	20			
3	4-2-28	EPL	54	F	Pernicious Anemia	69	259	02	136	3 gm tid	Duration 2 years Had previously eaten liver and taken Lilly's liver ext. Some general improvement—Numbness of extremities continues
	4-6-28					77	300	04		3 gm liver ext	
	4-11-28					80	286	22		tid (replaced spleen)	
	4-16-28					83	333	10		9 oz raw liver daily (replaced liver ext.)	
	4-20-28					87	296	24		3 vials Lilly's liver ext added to raw liver	
	4-25-28					85	289	32			
	4-30-28					91	333	37			
	5-4-28					93	342	30			
	5-21-28					96	370	19			

TABLE V, Continued

4	4-22-28 4-30-28 5-8-28 5-22-28	AA	72	F	Pernicious Anemia	58 66 74 90	186 237 306 403	16 110 140 80	152	3 gm tid	Duration (?)  Marked clinical improve- ment
5	6-15-28 6-21-28 6-29-28	GP	72	F	Pernicious Anemia	28 33 46	090 140 246	78 100 90	122	3 gm tid	Duration several months Marked clinical improve- ment
6	5-21-28 6-1-28 6-15-28 6-21-28 6-29-28	ST	55	F	Pernicious Anemia	45 58 64 80 84	180 196 221 342 349	10 40 134 70 50	117 114	3 gm tid	(Started 5-25-28) Marked parasthesias All parasthesias gone Marked clinical improve- ment





mal sources in the treatment of human anemias, we have been actuated mainly by the fact that our experience is at variance with the clinical reports thus far published by others. The experimental work of Leake, Bacon and Evans, Robschert-Robbins and Whipple and by ourselves (5), and the results obtained by McCann (6), all point to the belief that there are one or more factors common to bone marrow, spleen, liver, chicken blood cells, kidney, etc., which have similar hemopoietic effects upon the animal body. Nuclear extractives are common to all of these substances. The facts that such extractives obtained from the washed nuclei of chicken blood cells have this hemopoietic stimulant effect markedly and that the cytoplasm of the blood cell does not possess it at all are especially suggestive.

If we can tentatively conclude anything from our limited work, both clinical and experimental, it is that the hemopoietic stimulant, unknown as yet as to its composition, is an integral part of the cell nucleus, and

that the effect noted upon blood production from the taking of different animal tissues depends upon the amount of nuclear substance contained in that particular meat eaten. Liver has shown, in our experimental work, a greater stimulant effect than pancreas and thymus, but less than that of spleen, and the greatest effect, thus far noted, has been obtained from the washed nuclei of the blood cells from the fowl. A practical point may be suggested from this observation, namely, that liver alone, which is often repugnant to persons, may be replaced by the eating of kidney, sweetbreads, spleen and possibly beefsteak. The use of expensive pharmaceutical products may therefore be in part avoided.

One more point of importance seems to be logically deduced from our work. The results indicate a like response from the administration of these nuclear extractives in both primary and secondary anemias. Modifying factors may enter both groups and prevent or alter type blood reactions.

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- |   |  |
|---|--|
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| (2) J A M A, 1927, lxxix 682-685          | (5) Cited and reported J A M A, 1928, xc 75-78 |
| (3) J A M A, 1928, xc 75-78               | (6) Proc Soc Exp Biol & Med, 1928, xxv 255     |

# A Study of the Differential Blood Count in One Thousand Cases of Active Pulmonary Tuberculosis\*

By JOHN W. FLINN, *Prescott Arizona*

**T**HIS study was prompted by the work of Cunningham, Sabin et al, at the Johns Hopkins Hospital, on the rôle of the monocyte in experimental tuberculosis. After the study was begun, its scope was influenced very materially by the conclusions of Medlar and his co-workers at the University of Wisconsin, regarding the different parts played by the monocyte, the neutrophile and the lymphocyte in the histopathological reaction in tuberculosis.

Sabin and her associates, using supravital staining methods, traced the monocyte from its origin in the reticular cells of the spleen and of the bone-marrow to its consummation in the typical epithelioid cell of tuberculosis. As a result of a long series of observations in experimental tuberculosis they "think that a tuberculous process involves a marked new production and proliferation of monocytes in the tissues and their transformation into epithelioid cells."

Incidentally, they found that the transitional cell of the Ehrlich classification is in reality a more mature

form of mononuclear cell and is properly classed with the monocytes.

These investigators have also found that they "can quite accurately follow the course of the disease," in rabbits, "by the relative proportions of monocytes and lymphocytes in the circulating blood. When the animals have been killed at the time when the monocytes were markedly above the lymphocytes" they "have consistently found an extensive and active tuberculosis. In animals in which the tuberculosis had not become widespread, or in which the course of the disease was arrested as proved by autopsy" they "have found the lymphocytes in the circulating blood to be much more numerous than the monocytes."

Medlar and Kastlin in their experimental work corroborate the view that the monocyte "plays the chief rôle in the formation of the primary mononuclear or epithelioid tubercle." In addition, they made a very careful study of the part played by the polymorphonuclear leucocyte—the neutrophile—in the tissue reaction to the tubercle bacillus. They found this neutrophilic cell attracted to the scene of action after the monocytes had

\*Presented before the American College of Physicians, New Orleans, March 6, 1928

undergone necrosis, following an unsuccessful attempt to combat the infection. These neutrophils, through their proteolytic enzymes tend to liquefy the necrotic material and give rise to suppuration. If the neutrophils are killed, incomplete digestion of the dead connective tissue ensues and typical caseous material results.

These workers found that the lymphocytes are the cells principally concerned with healing in tuberculosis. If the healing occurs early with destruction of the tubercle bacilli, lymphocytes alone take part. If, however, healing occurs later, after suppuration and caseation have taken place, the lymphocytes are apparently aided by the monocytes in the healing process. It was the conclusions of these investigators that induced us to include the neutrophils in this study.

Our first reaction to the findings of Cunningham, Sabin et al, regarding the monocyte-lymphocyte ratio in the circulating blood of tuberculous animals was a desire to investigate this ratio in tuberculosis in man. Our thought was to carry on a series of observations on routine patients, using supravital staining methods. We found these methods so time-consuming, however, that we were forced to abandon this plan.

It then occurred to us to use the records, which have been accumulating in our office for many years, of routine blood examinations of patients in all stages of pulmonary tuberculosis, and to make an intensive study of the blood-picture in one thousand of these patients. It is true that these counts were made from

fixed films stained with Wright's stain, but we believe they are sufficiently accurate for practical purposes. Using these records gave us access to a much larger number of cases than we could possibly accumulate in a short time. Moreover, since these were routine counts, by different technicians, made with no thought of proving anything in particular, they probably represent a fairly accurate cross-section of typical blood pictures in active pulmonary tuberculosis.

We were soon faced with the question whether a consideration of the percentages of monocytes, neutrophils and lymphocytes was sufficient, or whether it was advisable to calculate the numbers of these cells per cubic millimeter. This seemed to us a rather important question, since percentages can be calculated from dried films which can, if necessary, be sent to a distant laboratory, while total white counts and numbers of monocytes, neutrophils and lymphocytes per  $\text{cmm}$  can be made only from freshly drawn blood specimens.

Finally we compromised between these two positions. We took the blood pictures from three hundred and fifty cases examined in the war period when laboratory technicians were scarce, and when we were forced to send blood specimens to a laboratory in a distant town. In these we have only the percentages of monocytes, neutrophils and lymphocytes recorded, and the conclusions in these three hundred and fifty cases are based solely on these percentages. Over against these we placed the records of six hundred and fifty cases in which the blood counts were made

in our own laboratory and included total leucocyte counts and numbers and percentages of monocytes, neutrophils and lymphocytes

In our monocyte count we included the large and the small mononuclears and the transitionals of the Ehrlich classification. Neither the eosinophiles nor the basophiles are included in this study

In the classification of cases we used the plan adopted by the National Tuberculosis Association as a basis. The first two divisions of this classification were adopted as outlined—the minimal and the moderately advanced. From the third class—far advanced—of the National Tuberculosis Association, a fourth class—“very far advanced—probably hopeless” was taken. This gave us four classes: I Minimal, II Moderately Advanced, III Far Advanced, IV Very far Advanced, probably hopeless.

Chart I shows the average numbers of monocytes, neutrophils and lymphocytes per cubic millimeter in each of the four different classes of the six hundred and fifty-one cases of the second part of this study. It also records the monocyte-lymphocyte ratio and the lymphocyte-neutrophile ratio in these different averages. These calculations included twelve hundred and forty-six blood counts in six hundred and fifty-one cases. In class I, the minimal class, there were 125 cases and 215 blood counts. In class II, the moderately advanced class, there were 257 cases and 565 blood counts. In class III, the far advanced—probably hopeless—class—

there were 49 cases and 76 blood counts.

The average monocyte count per cubic millimeter was 159 in the minimal class. It increased to 183 in the moderately advanced class, to 340 in the far advanced, and to 516 in the very far advanced class. In other words the average monocyte count per cu mm *increased* steadily until it was  $3\frac{1}{4}$  times greater in the very far advanced cases, than in those cases showing only a minimal lesion.

The average neutrophile count per cubic millimeter was 4161 in the minimal class. It increased to 5055 in the moderately advanced class, to 6952 in the far advanced class, to 8880 in the very far advanced class. In other words the average neutrophile count per cu mm *increased* steadily until it was more than  $2\frac{1}{10}$  times greater in the very far advanced cases than in the minimal class.

The average lymphocyte count per cu mm was 2664 in the minimal class. It increased to 2898 in the moderately advanced class and then decreased to 2781 in the far advanced class. It decreased still further—to 2460—in the very far advanced class. In other words the average lymphocyte count per cu mm did not vary nearly so greatly and not so consistently as did the average monocyte and the average neutrophile counts.

The average percentage of monocytes increased from 21% in the minimal class to 29% in the moderately advanced class. It further increased to 33% in the far advanced class, and to 43% in the very far advanced class. In other words the average percentage of monocytes was

## Composite Blood Picture With Leucocyte Count

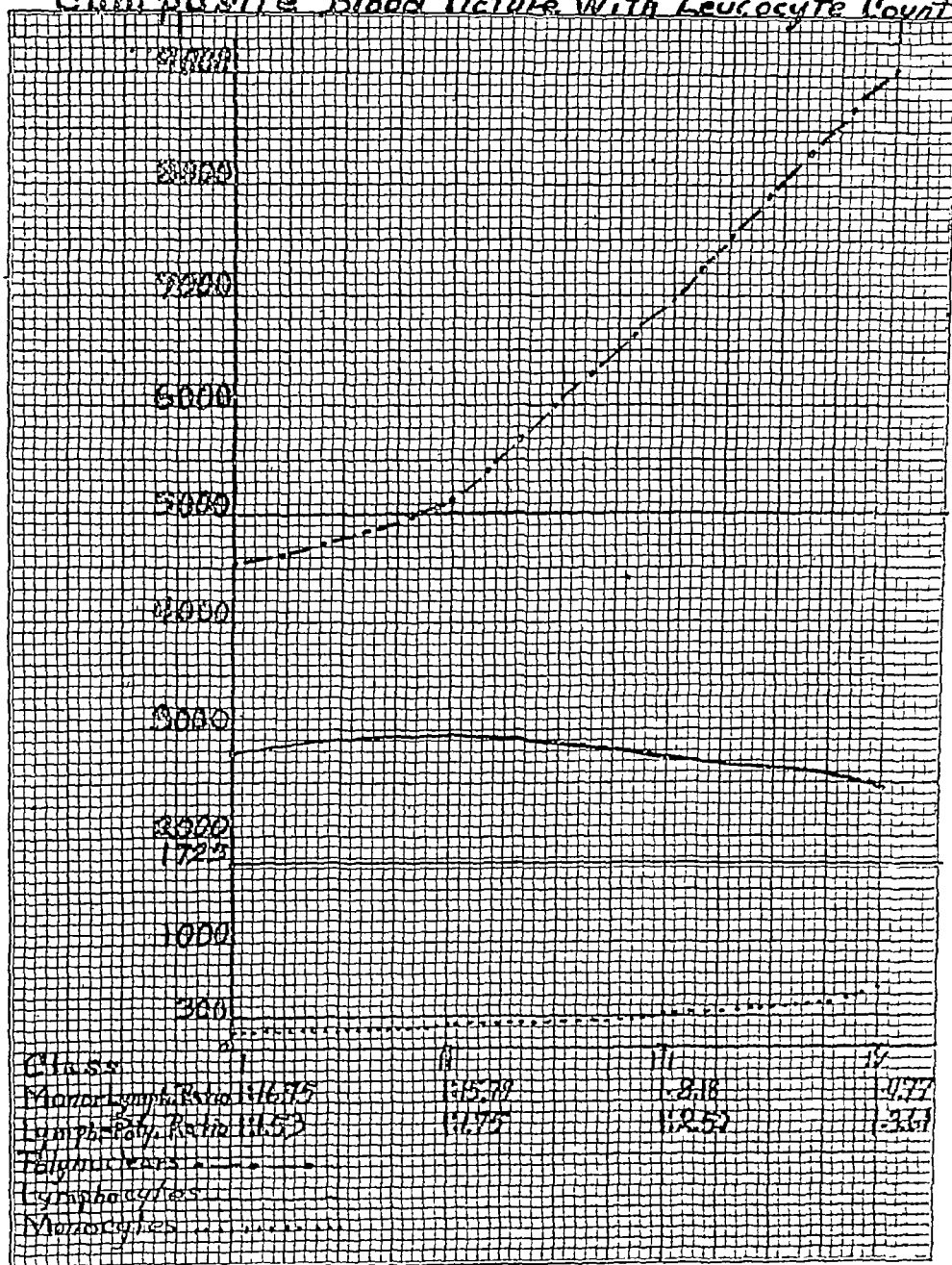


CHART I

more than twice as great in the fourth class as in the first class.

The lymphocytes decreased from 36.3% in Class I to 34.5% in Class II, to 27.2% in Class III, and to 20.5% in Class IV. In other words the average percentage of lymphocytes decreased steadily and markedly until the percentage in the far advanced cases was down nearly to one half the percentage in the minimal cases. In general there was a noticeable increase in the percentages of both monocytes and neutrophils and a more marked decrease in the percentage of lymphocytes as these cases progressed from the minimal to the very far advanced stage.

The average monocyte-lymphocyte ratio and the average lymphocyte-neutrophil ratio calculated from the cubic millimeter counts in these 651 cases showed more marked changes in each class, than did either the average total cubic millimeter count or the average percentage calculation. The average monocyte-lymphocyte ratio in Class I was 1.1675, in Class II it was 1.1578, in Class III 1.818, and in Class IV 1.477. In other words the ratio of lymphocytes to monocytes had decreased in the very far advanced cases to almost one quarter of what it was in the minimal cases. The average lymphocyte-neutrophil ratio in Class I was 1.153, in Class II it was 1.175, in Class III 1.250, and in Class IV 1.361. In other words the ratio of neutrophils to lymphocytes increased in the very far advanced cases to more than  $2\frac{1}{2}$  times greater than in the minimal cases.

To summarize the results of the

study of the average counts in the 651 cases in which the blood counts were made in our own laboratory and included total lymphocyte counts and numbers and percentages of monocytes, neutrophils and lymphocytes

(1) The average number of monocytes and neutrophils per cu mm increases noticeably as the disease becomes more advanced, the increase in monocytes being proportionately the greater increase of the two.

(2) The average number of lymphocytes per cu mm at first increases slightly as the disease advances. It then slowly decreases and towards the end decreases quite rapidly.

(3) The average percentages of monocytes and of neutrophils increase noticeably as the disease becomes more advanced, the increase in the percentage of monocytes being proportionately the greater of the two.

(4) The average percentage of lymphocytes decreases very noticeably as the disease becomes more advanced, the decrease being almost as great proportionately as is the increase in monocytes.

(5) The most marked changes are found in the monocyte-lymphocyte and the lymphocyte-neutrophil ratios, as calculated from the cu mm counts. The monocyte-lymphocyte ratio decreases very considerably as the disease becomes more advanced, while the lymphocyte-neutrophil ratio increases almost as greatly.

Chart II shows the average percentages of monocytes, neutrophils and lymphocytes in each of the four different classes in 345 cases of the first part of this study. It also re-

*Composite Blood Picture Without Leucocytes*

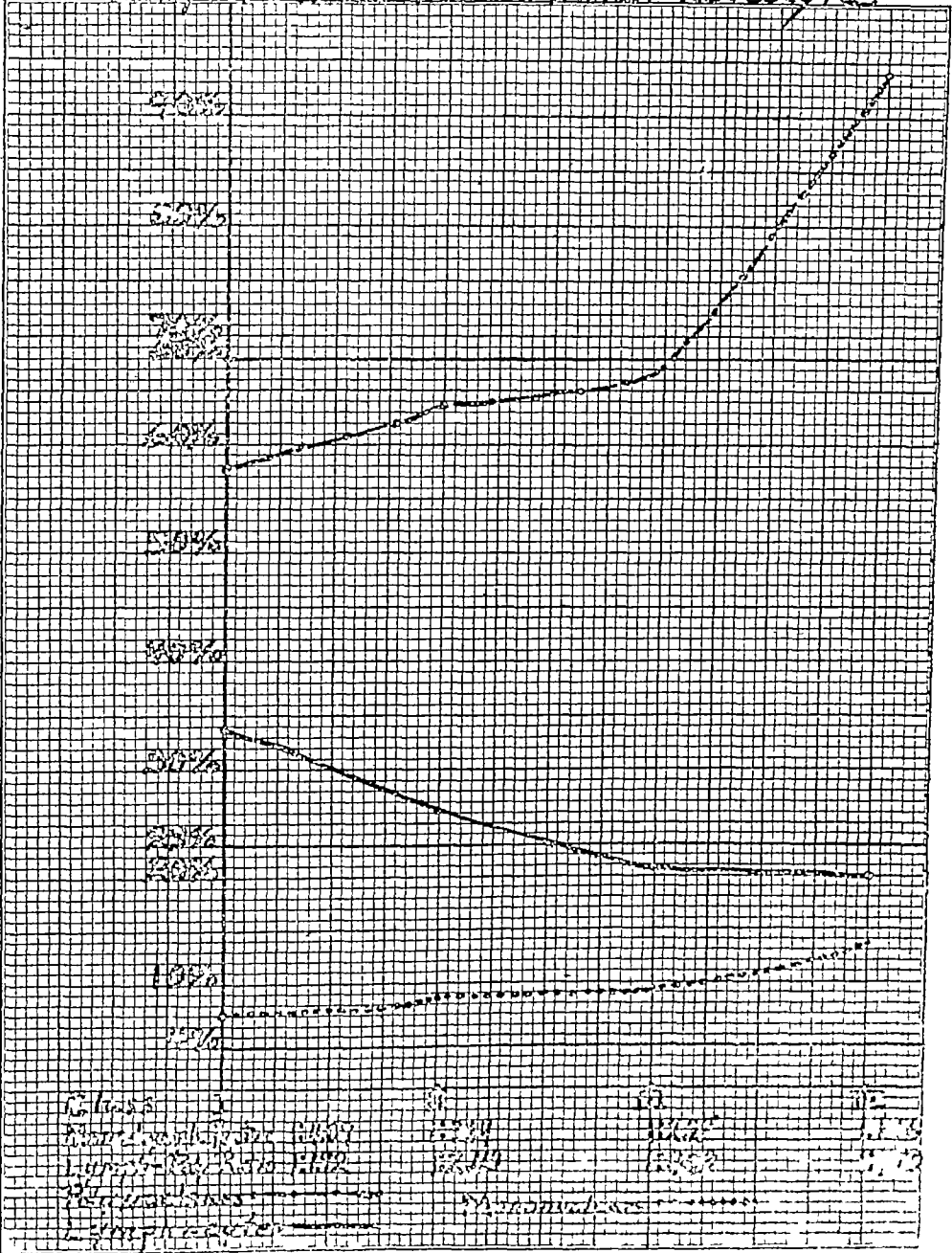


CHART II



cords the monocyte-lymphocyte ratio and the lymphocyte-neutrophile ratio in these different averages

These calculations include 632 blood counts in 345 cases. In Class I—the minimal class—there were 35 cases and 59 blood counts, in Class II—the moderately advanced class—there were 163 cases and 298 blood counts, in Class III—the far advanced class—there were 140 cases and 266 blood counts, in Class IV—the very far advanced, probably hopeless class—there were seven cases and nine blood counts

The average percentage of monocytes was 7.6% in the minimal class. It *increased* to 8.3% in the moderately advanced class, to 9.1% in the far advanced class, and to 13.7% in the very far advanced class. In other words the average percentage of monocytes increased steadily until in the fourth class this percentage was almost double what it was in Class I.

The average percentage of neutrophiles was 57.9% in Class I. It increased to 63.5% in Class II, to 68.9% in Class III, and to 94% in Class IV. In other words the average percentage of neutrophiles increased steadily until in the fourth class this percentage was more than 50% greater than in Class I.

The average percentage of lymphocytes was 33.9% in Class I. It decreased to 26.4% in Class II, to 20.7% in Class III, and to 20% in Class IV. In other words the average percentage of lymphocytes decreased steadily until in the fourth class it was more than 33% less than in Class I.

The monocyte-lymphocyte ratio and the lymphocyte-neutrophile ratio showed even more marked changes in this series also. The monocyte-lymphocyte ratio was 1.409 in Class I. It *decreased* to 1.314 in Class II, to 1.228 in Class III, and to 1.146 in Class IV. The lymphocyte-neutrophile ratio was 1.192 in Class I, *increased* to 1.240 in Class II, to 1.429 in Class III and to 1.470 in Class IV.

The summary of the results in the average percentages and in the monocyte-lymphocyte and the lymphocyte-neutrophile ratios in the previous series of 651 cases applies equally well to this series of 345 cases in which only differential counts on dried films were made. This striking similarity of results seems all the more remarkable when the noticeably different percentages of monocytes and of lymphocytes in the same classes in the two series of cases is observed. This was evidently due to different systems of identifying different mononuclear cells. The technicians in the series of 345 cases undoubtedly classified many cells as monocytes which those who examined the blood in the 651 cases identified as lymphocytes. And yet, as noted above, the averages correspond very closely.

Chart III shows three differential blood counts on a far advanced case of pulmonary tuberculosis which improved rather remarkably under quite prolonged bed-rest and subsequent very carefully graduated exercise. In May 1925 this patient had extensive active involvement in all lobes of one lung with rather slight active disease in the upper lobe of the other lung. At that time she had a very high

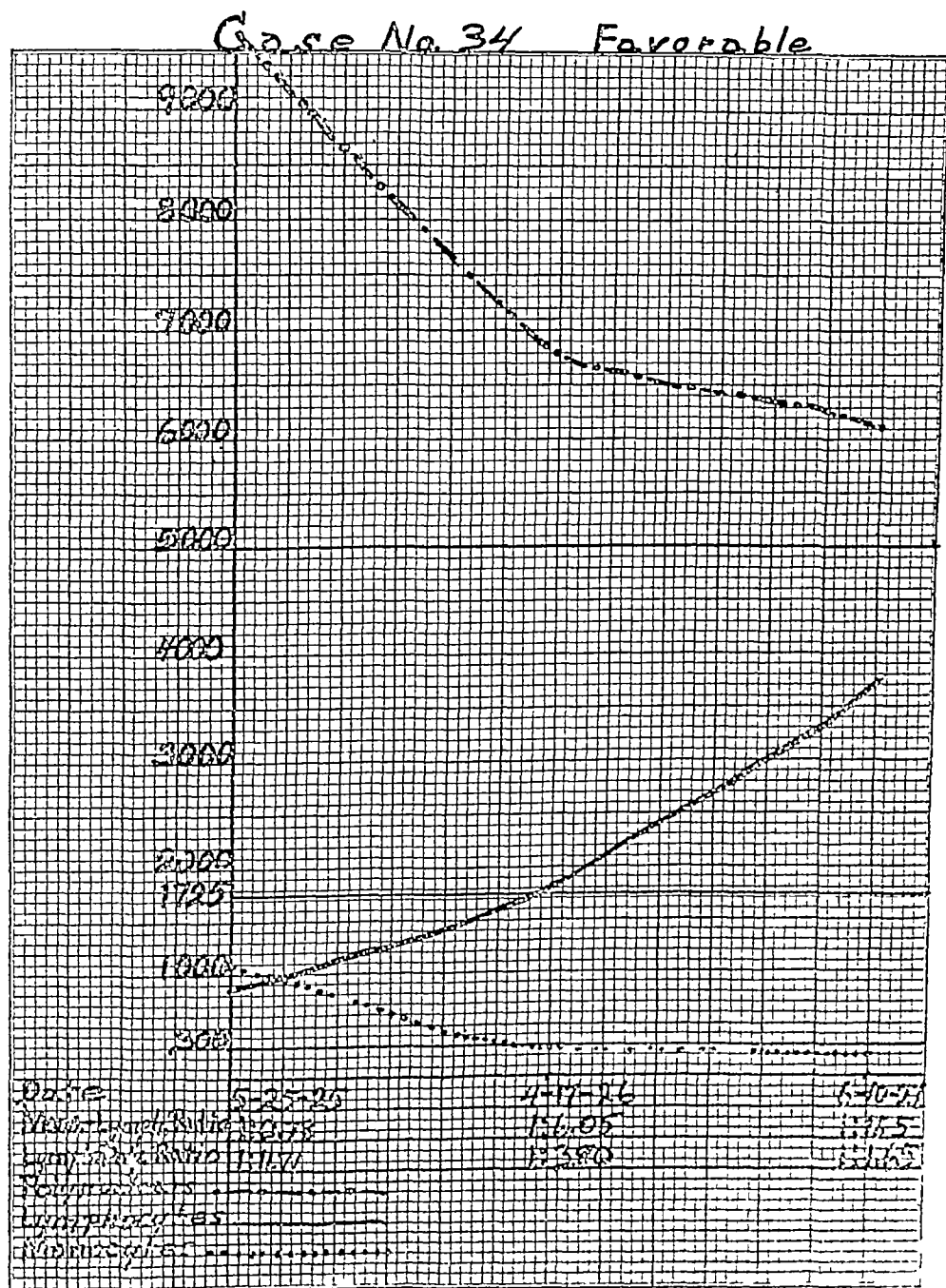


CHART III

monocyte count (above 1,000 per cu mm) a very high neutrophile count (above 9,000) and a very low lymphocyte count (below 1,000). After one year's rest in bed her lung condition and symptoms had improved rather markedly. At the same time the monocytes and neutrophiles had noticeably decreased and there had been a similar increase in the number of lymphocytes. At the end of another year, spent on very carefully graduated exercise, the symptoms had disappeared, the lung condition was almost quiescent and the leucocytic picture showed still further improvement. Corresponding changes are noted in the monocyte-lymphocyte and in the lymphocyte-neutrophile ratios.

In this case—an exceptionally favorable one—the leucocytic picture runs absolutely true to the form laid down in the composite graphs. The monocytes and the neutrophiles decrease steadily and consistently from beginning to end, and the lymphocyte-neutrophile ratio shows a corresponding *decrease*. On the other hand a similar *increase* is seen in the lymphocyte count and in the monocyte-lymphocyte ratio.

Chart IV shows a more complicated blood-picture in a case which ran a stormy and uncertain course for some time before finally settling down to a fairly satisfactory improvement. This case was admitted in May 1924 with extensive involvement of the right lung throughout, and a history of sudden onset and rapid extension of the disease. One month's rest in bed produced some slight improvement in the symptoms and in the lung findings. This was accom-

panied by a very satisfactory decrease in the monocyte and the neutrophile counts, and a slight decrease in the lymphocyte-neutrophile ratio. The lymphocyte count, however, did not increase, but it decreased somewhat. The monocyte-lymphocyte ratio too was quite unsatisfactory. Instead of increasing, it decreased to less than one-half.

For the next five months (June to November) this patient did rather badly. The symptoms grew slowly worse and the lung signs increased. During this period the neutrophile count increased greatly. The monocyte count varied with a distinct general trend upward. The lymphocyte count at first increased somewhat and then took a marked drop. The monocyte-lymphocyte ratio increased and then decreased somewhat. The lymphocyte-neutrophile ratio increased greatly.

During the next six weeks (November to January) the patient's symptoms improved, but examination of the chest showed slight activity in the upper lobe of the left lung. It is noticeable that during this period the monocyte count increased although the leucocyte picture improved in every other respect. We then did a successful artificial pneumothorax after which the patient made uncertain but fairly satisfactory improvement. Today she is quite free of symptoms with the lung still compressed.

Chart V shows a leucocytic picture which runs true to form in every respect, except one—the lymphocyte count has not increased satisfactorily. This patient first came under observation in October 1927 with extensive

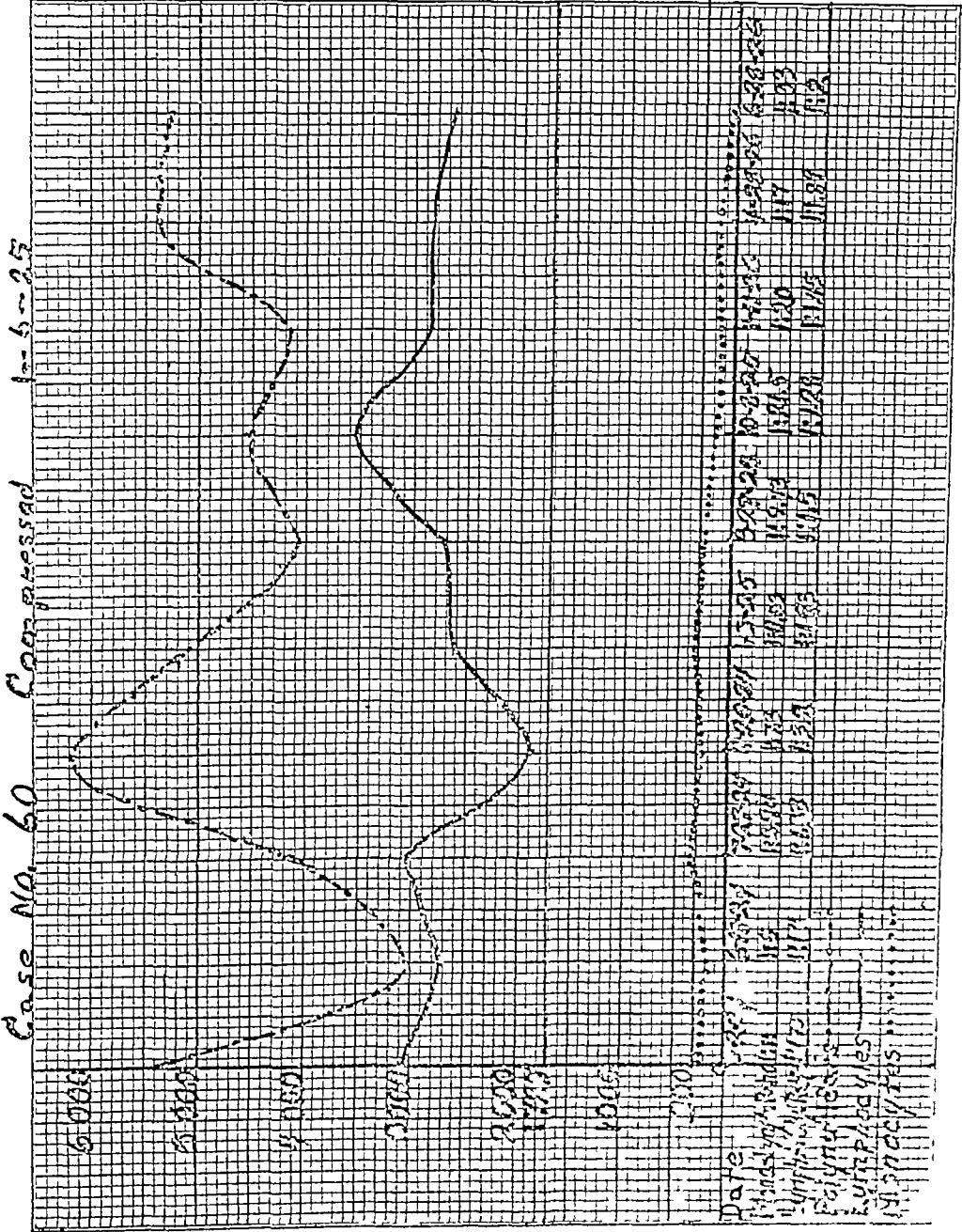


CHART IV

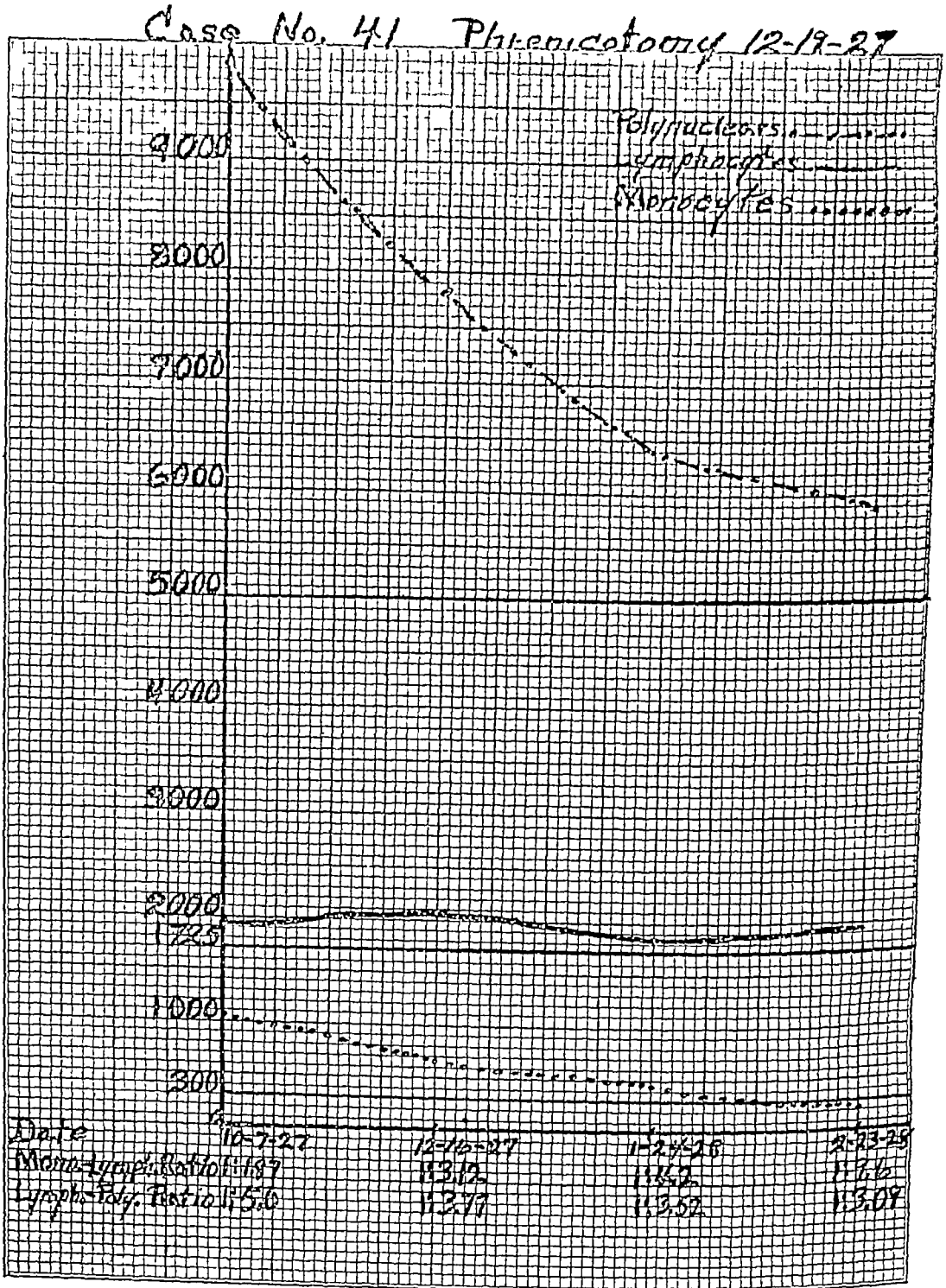


CHART V

involvement in the right lung throughout. In addition she had very slight low grade active disease in the left upper lobe and the laryngologist reported a suspicious throat. We at once attempted an artificial pneumothorax, but failed after repeated attempts. We then did a right phrenicotomy, since when the patient has improved noticeably, under fairly complete bed-rest. We still consider the outlook for this case doubtful and are inclined to think that a thoracoplasty will be indicated.

Chart VI shows the leucocytic picture of a quite acute case of far advanced unilateral pulmonary tuberculosis which came under observation in February 1925 and ran an unsatisfactory course, under bed-rest, for a full year. In the meantime pneumothorax was attempted, but unsuccessfully. At the end of a year a thoracoplasty was performed, although it did not seem to be a very suitable case for this operation. Since then her condition has improved fairly satisfactorily. Since the thoracoplasty there has been a satisfactory *decrease* in the monocyte count, the neutrophile count and the lymphocyte-neutrophile ratio. There has also been a satisfactory increase in the monocyte-lymphocyte ratio. The increase in the lymphocyte count, however, has not been quite satisfactory. We expect a permanent improvement in this case, but consider it doubtful if the disease will ever become quite quiescent.

Chart VII shows the pictures of a very far advanced case of pulmonary tuberculosis which was classed as probably hopeless when the patient first came under our observation in

May 1927. The striking feature of this graph is the steady and persistent increase in the monocyte count with a corresponding decrease in the lymphocyte count, until these two counts are nearly equal at the time of the last examination. This is indicated too by the fact that the monocyte-lymphocyte ratio has decreased from 1.35 to 1.1—nearly thirty-five fold. The neutrophile count in this case is fairly characteristic, as is also the lymphocyte-neutrophile ratio.

#### CONCLUSIONS

1. A full leucocytic picture, including total numbers per cubic millimeter, and percentages of monocytes, neutrophiles and lymphocytes is a very important part of every examination of a tuberculous patient. This information is *always* very helpful in diagnosis, prognosis and treatment, and often gives a truer conception of the pathology of the case than any other part of the examination.

2. The monocyte-lymphocyte and the lymphocyte-neutrophile ratios (of either the numbers per cu mm or of the percentages) seem to us to give the truest conception of the status and progress of the case. The percentages in themselves seem the next most reliable indication. The numbers per cubic millimeter although interesting and helpful, seem to us the least important of these three classes of observations.

3. A decreasing monocyte-lymphocyte ratio and an increasing lymphocyte-neutrophile ratio point very definitely to a more active and extensive lesion. The converse points just as

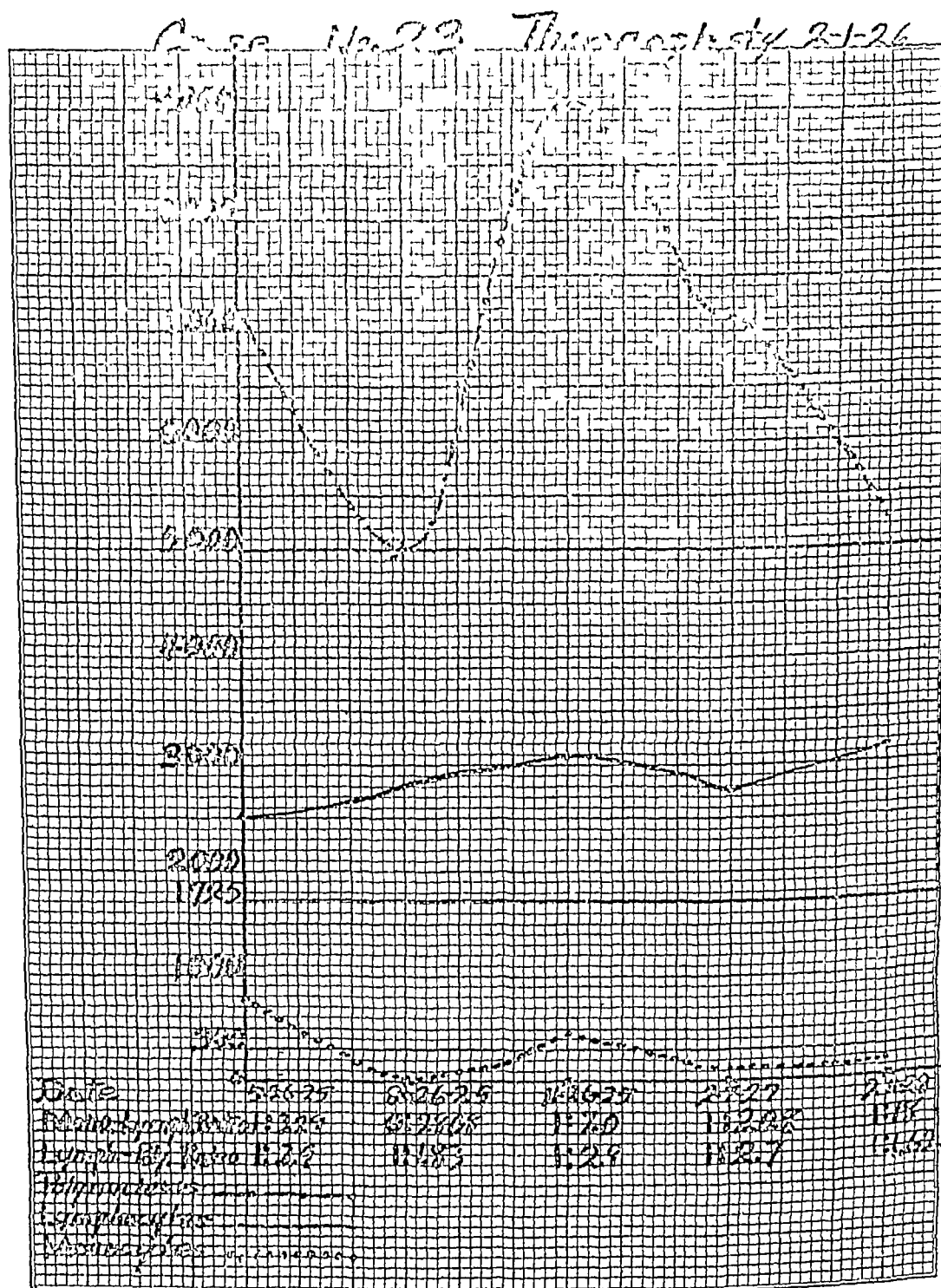


CHART VI

definitely to an improved lung condition

4 An increase in the percentages

of neutrophils and of monocytes, with a decrease in the percentage of lymphocytes points quite definitely to a more active and extensive lesion

The converse points quite definitely to an improved lung condition

Corresponding changes in the counts per cu mm of these cells point in corresponding directions, but less definitely

5 This study tends to corroborate clinically the experimental work of

The writer wishes to acknowledge with thanks his indebtedness to Mr Theodore W Keiper, A B in charge of the Parnestgaaf Laboratory, and to Mr Ernest Born, B S and Mr O P Shook, Jr, for very valuable assistance in the technical and mechanical parts of this study

reaction in tuberculosis

Cunningham, Sabin et al, on the significance of the monocyte-lymphocyte ratio in the circulating blood of the tuberculous, and to confirm the conclusions of Medlar and his associates regarding the different parts played by the monocyte, the neutrophil and the lymphocyte in the histopathological



# Rheumatic Fever: Clinical Manifestations, Etiology, and Treatment\*

By DAVID RIESMAN, M D , Sc D , and JAMES CRAIG SMALL, M D , Sc D ,  
*Philadelphia*

WE DESIRE to discuss rheumatic fever under three aspects

## I Clinical Manifestations

## II Etiology

## III Treatment

I The clinical manifestations subsumed under the name of rheumatism are exceedingly numerous Wiesel (*Med Klin* 1923, xix, 163), found a total of eighty different pathological conditions included under the term rheumatism, we shall limit ourselves to ten, as follows

- 1 Articular rheumatism or better acute rheumatic fever
- 2 Some forms of tonsillitis and pharyngitis
- 3 Chorea minor
- 4 Cerebral rheumatism or rheumatic hyperpyrexia
- 5 Certain types of heart disease
- 6 Certain forms of muscular pains, growing pains in children, some forms of neuritis

- 7 Various skin manifestations
  - a Rheumatic nodules
  - b Erythema multiforme
  - c Rheumatic purpura (peliosis rheumatica)
- 8 Certain forms of chronic arthritis, usually following recurrences of rheumatic arthritis
- 9 Pleuritis
- 10 Pneumonia

There is evidence, in many instances purely circumstantial, upon the basis of which clinicians believe themselves justified in calling this heterogeneous group, rheumatic. But if to this group of seemingly diverse morbid conditions the term "rheumatic" is to be correctly applied, it can be done only on one condition—that they all prove to have the same etiology or that they all respond to the same specific treatment. Hitherto they have been placed together by nosographers solely on clinical grounds which it may be well to enumerate

1 The less clearly defined conditions occur in persons who have had characteristic attacks of rheumatic fever. They are more or less influenced by atmospheric changes

2 Tonsillitis is a frequent antecedent of rheumatic fever. In Swift's

\*Read at the meeting of the American Association of Physicians in Washington, May 1928



ity is not an important factor in the spread of rheumatic fever, but that, as was demonstrated by St Lawrence, (Journal of the American Medical Association, 79, 2051, December 16, 1922) contagion plays a rôle similar to that in tuberculosis Grenet (Sem des hôp 3 288, May, 1927) reports five distinct epidemics and there are records of multiple cases in the same household

The influence of environment is also evident, the disease being distinctly rarer in children of the so-called better class of families Among environmental influences must be mentioned climate The potency of this is shown by Harrison and Levine, (Southern Medical Journal, December 1924) who found that rheumatism and rheumatic heart disease are much more common in Boston than in cities of the South

The anatomic lesions of rheumatic fever deserve to be discussed as they throw light upon the clinical aspects of the disease They are principally of two types Proliferative and exudative The latter are represented by the outpouring of serum into the joints and peri-articular tissues, pericardium and pleura, the former, by the so-called Aschoff bodies which most writers consider pathognomonic of rheumatic infection (not Friedrich von Muller, Am J Med Sc, January, 1928) \*

They consist of collections of cells mostly of irritation or giant cell type differing however from those of the tubercle While these nodules are seen

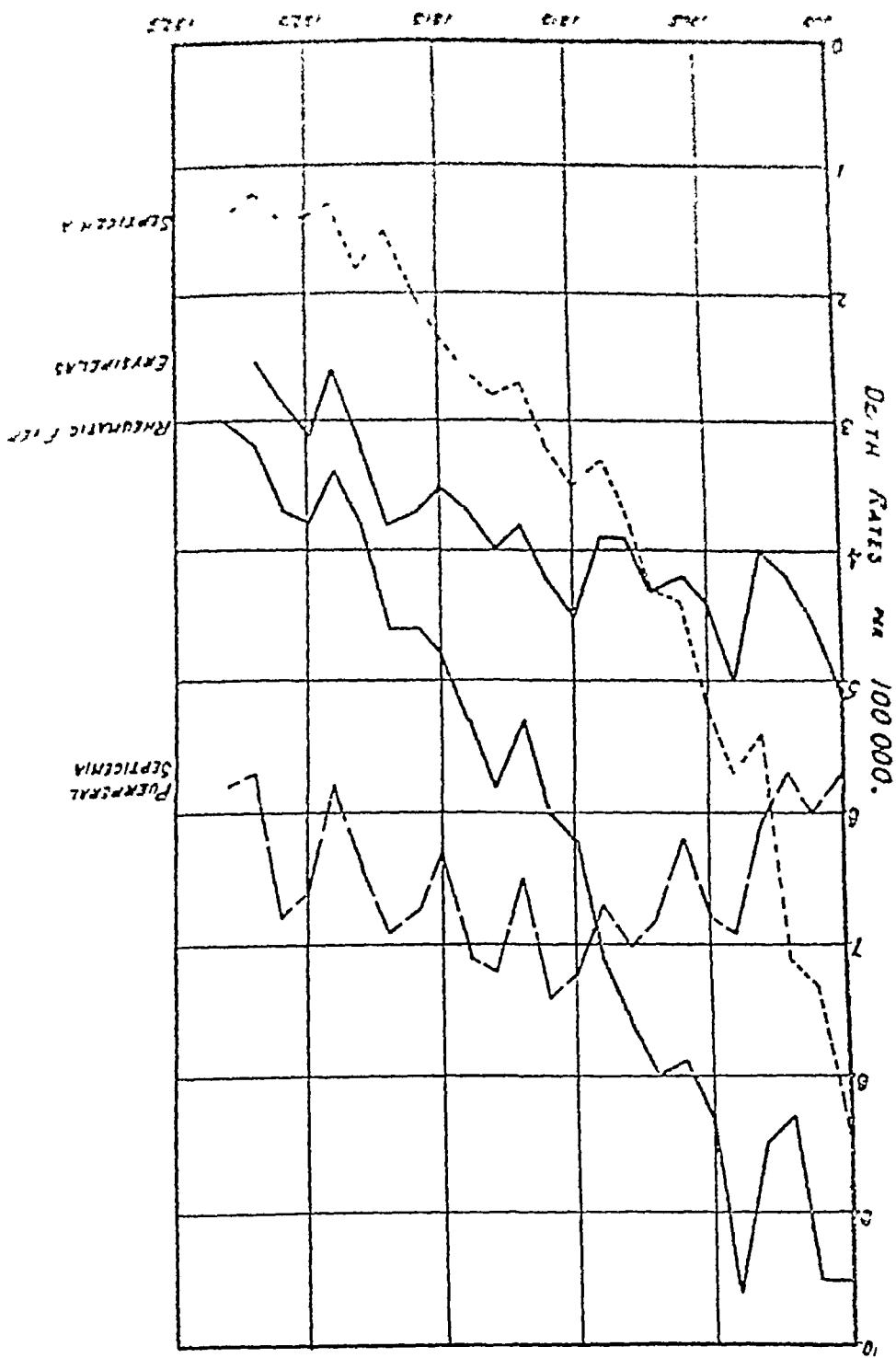
\*They have recently been described in meningococcus infection (Rhoads, Am J Path, 1927, 3, 623)

most characteristically in the heart muscle and in the rheumatic subcutaneous nodules they are also found in a modified form in the diseased valves, in the subserous layers of the inflamed pericardium, in the aorta (Pappenheimer and von Glahn, Journal of Medical Research, 1924, 44, 489), and in the brain in chorea This last discovery, made by Poynton and Holmes, (Lancet, October 13, 1906, 982) at an early day is a strong argument in favor of the belief that chorea is due to an encephalitic rheumatic process which at times may be associated with meningitis (Swift, Am J Med Sc, November, 1924)

### ETIOLOGY

That rheumatic fever is an infectious disease cannot be doubted There is even evidence, as already mentioned, of a certain mild contagiousness Its seasonal prevalence corresponds to that of the acute respiratory infections Frequently the disease is inaugurated by an attack of tonsillitis or pharyngitis Atwater (see chart I) has recently shown (Am Jour Hygiene, May, 1927) that epidemiologically the incidence of rheumatic fever closely parallels that of the well-known streptococcus infections of scarlet fever, erysipelas, puerperal septicemia

The association of a streptococcus with rheumatic fever was first observed by Poynton and Payne in 1900 Blood cultures in the acute attacks of rheumatic fever are sterile as a rule In January, 1927, attention was directed by one of us (J C S) to a streptococcus isolated from the blood of a typical case of rheumatic fever



Studies of this organism showed that it belonged to a distinct immunologic species. It was furthermore easy to isolate it from throat cultures of patients with rheumatic fever. It was also obtained from the cultures of the feces of some cases of chronic arthritis. The organism has been described under the name *Streptococcus cardioarthritidis*, (Small, J. C., Am J Med Sc 1927, 173, 101). Further studies have shown its wide-spread distribution, the lesions produced by it in experimental animals, Belk, Jodziss, and Friedrich (Arch Pathology, in press), and the appearance of immune bodies in the blood of patients with rheumatic fever, chorea, etc. The therapeutic application of antiserum, of vaccines, and of soluble products derived from the microorganism have also been investigated.

Strains of this streptococcus constitute the first compact serologic group found definitely associated with rheumatic fever (Kreidler, W. A., Jour Infect Dis, in press).

The organism is most readily obtained from throat cultures of patients with acute rheumatic fever and chorea. The mode of collecting material for such cultures is important. No attempt should be made to obtain material from the tonsillar crypts if the tonsils are intact. Material from the crypts ordinarily shows an abundant growth of streptococcus viridans, streptococcus haemolyticus and other bacteria. It is not the best source from which to obtain primary cultures of the streptococcus cardioarthritidis. The organism prefers the superficial sites in the pharynx—hence it is best to obtain the material

on a sterile swab from the reddened streaks of the mucous membrane of the anterior pillars, uvula, or soft palate. We would make the suggestion that the peculiar superficial inflammation which constitutes the so-called rheumatic throat of the older clinicians may be dependent upon infection with this streptococcus. The throat that we have come to regard as associated with acute rheumatic fever and which yields the most abundant growth of the streptococcus in primary cultures might perhaps be described at this point.

The striking clinical feature in the throat in the acute phase of rheumatic fever appears in areas of intense redness of the mucous membrane of the anterior pharyngeal pillars on either side, which unite at the uvula, thus presenting an inverted crescent-shaped area of inflammation. In the most intense inflammatory reactions, this area spreads forward over the soft palate for a third to a half of its extent. Over the soft palate intensely congested small blood vessels stand out prominently. The inflammation appears to be very superficial. There is no tendency to ulceration, necrosis or the formation of an opaque exudate. Transparent mucus, in slight excess perhaps, may be collected upon swabbing such areas. The color of the inflamed mucous membrane is a very brilliant red during the acute stage, later as these areas recede the palate and uvula take on a bluish red color. The bluish red areas appear as vertical streaks on the anterior pillars and do not unite above to complete the crescent-shaped area. In the acute stages the brilliant red



certain phases of the disease. Nor will we dwell on the use of non-specific proteins since their very name indicates that they are not what science is looking for.

Menzer in 1902 reported favorable results from polyvalent antistreptococcal serum and looked upon the immediate febrile reaction as well as upon the later serum disease as factors influencing the results obtained.

For about 18 months antiserum (Rheumatic Fever, I & II, Small, J. C., *Am J Med Sc*, 1928, 175, 638) prepared by immunizing horses with the *Streptococcus cardioarthritidis* has been in use and has been employed in the treatment of upwards of 270 patients in the Philadelphia General Hospital. For the past year special wards set aside for the study of rheumatic fever have aided greatly in the collection of observations upon which to base the present estimate of the efficacy of the treatment.

The serum was employed first in chorea and acute rheumatic fever, later also in certain forms of chronic arthritis in an effort to determine the relationship if any between these forms and acute rheumatic fever.

The antiserum has been prepared in horses and more recently in cattle—the two appear to be equally effective in treatment. The use of the bovine serum has been followed by very mild serum disease, hence it is preferable to equine serum which frequently calls forth a rather severe serum sickness. Since November 1927 a concentrated antiserum has been available. The amount to be injected is still empiric as so far no method has been developed for determining

the relative antibody content of the different lots of serum. Experience has shown that the antisera now being produced are of such potency that the adequate dose ranges from 5 to 15 cc. Excessive amounts have not been followed by the definite alleviation of the joint symptoms or by that decline of temperature which had followed the use of smaller and seemingly adequate amounts. This paradoxical sequence of events following excessive doses has been attributed to focal inflammatory reactions arising at the sites of the union of antigen and antibody in such amounts as to give rise to a reaction similar to the Arthus phenomenon. In practice these focal reactions are prevented by avoiding the injection of excessive amounts of antibody and by administering the estimated adequate amounts of antibody in fractional doses, allowing from 12 to 18 hours to elapse between the injections of the several doses.

The focal reactions have not been noted in our limited observations upon private patients who were under full doses of salicylates at the time the serum was administered. Moreover focal reactions well established have responded to the administration of moderate doses of salicylates in from 18 to 24 hours.

A much more important phase of the treatment of the rheumatic diseases is concerned with the problem of active immunization. In general passive immunity conferred by an antiserum is of short duration, active immunity conferred by vaccines or by antigenic products of bacteria is of a

more lasting character Rheumatic fever as a chronic continuing disease of the heart could scarcely be expected to respond adequately to serotherapy We believe that relapses following serotherapy can be greatly reduced by the use of repeated injections of small amounts of vaccine or of the soluble products of *Streptococcus cardioarthritidis* We have reason to believe that this combination constitutes an effective prophylactic therapeutic procedure in the rheumatic diseases

The soluble antigen of *Streptococcus cardioarthritidis* in dilutions of 1:10,000 and 1:1,000 is the agent at present employed in attempts at active

immunization The 1:10,000 dilution is used in initial doses of not more than 0.5 cc. and maintained at this amount until no reaction following its injection can be detected After that the doses are gradually increased by from 25 to 50% of the dose last given The injections are administered subcutaneously and at intervals of from 5 to 7 days The soluble antigen should be employed routinely in patients treated with antiserum The injections may be started as early as the third day or may be delayed until after the period of serum disease has passed In the subacute and chronic forms the antigen alone may be used



# The Dietetic Treatment of Diabetes Mellitus\*†

## A Restatement of the Fundamental Principles

By L. H. NEWBURGH, *Ann Arbor*

**A**S long ago as 1914, F. M. Allen had demonstrated that the principle of undernutrition was vastly more successful in the reduction of diabetic hyperglycemia and glycosuria than the older methods in use at that time. Joslin enthusiastically adopted this principle and made it the central feature in the routine treatment of his diabetic patients. Both men emphasized the value of a sharp reduction of calories, but paid little attention to the source of the energy of the diet, with the exception that they permitted only minimal amounts of fat. Joslin felt it necessary to keep the fat as low as possible as a safeguard against acidosis and Allen in one of his publications stated that "fat is a poison for the diabetic."

In order to appreciate the great value of low calory diets it is necessary to recall to mind the composition of the diets in general use during the preceding era. From time immemorial it has been good practice to build up the body of the sick individ-

ual, and no exception was made in the case of the diabetic. In fact it was considered essential to add large increments to the weight of these patients, in order to counteract the emaciation so characteristic of that disease. In the second place every attempt was made to avoid carbohydrate. A typical diet of those days consisted of 200 grams of protein, 200 grams of fat, and a small amount of carbohydrate. The patient received some 2700 calories and very frequently continued to have a glycosuria. The therapeutic failure was attributed by Allen to excess of calories, but another and simpler explanation was brought to light by estimating the glucose value of the diet by Wood-yatt's method. When this is done it is found that the sort of diet just described contains 150 grams, or more, of available glucose. Need we be surprised that all but the mildest diabetics continued to excrete sugar in the urine while living on such a diet?

If now the type of diet used by Allen and Joslin be analyzed in the same way, its great advantage is easily understood. Such a diet might have the following composition: Protein 50 grams, Fat 30 grams, Carbohydrate 50 grams, with a glucose value of only 80 grams. Most dia-

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†Presented to the Michigan State Medical Society at its annual meeting in Detroit, September 28.



uncomplicated cases" This statement was published in 1923 The continued employment of the plan has merely strengthened our confidence in it

It need scarcely be added that the administration of insulin, increases the responsibility of adhering strictly to proper dietetic principles Everyone recognizes the life-saving quality of insulin in the treatment of diabetic coma On the other hand, in the routine treatment of the controlled diabetic it should only be used to aid the patient in obtaining sufficient energy for maintenance when a diet containing his caloric requirement causes glycosuria This conclusion is based on the conviction that insulin increases quantitatively the total amount of internal secretion but is in no sense curative If the physician will employ the kind of diet described above he will find that four fifths of his adult patients do not need insulin In the case of children, because of their much greater caloric requirement, insulin is necessary to promote normal growth in most of these patients During the past year we prescribed diets for 347 diabetic patients Two hundred and fifty six of them, or 74% were able to take a maintenance diet of 2200 calories or more, without insulin The total glucose of the diet was at least 90 grams

It needs to be emphasized that the low protein, low carbohydrate, high fat, maintenance diet, is the inevitable result of the application of the laws of nutrition to the special metabolic problem of the diabetic With this simple fact in mind, we can not avoid regarding Joslin's (1) recent adverse

criticism of this dietetic procedure as an unjustifiable interference with a method that is working well He finds that 47% of his 609 diabetic deaths since the introduction of insulin were due to disease of the arteries (we refrain from questioning how many of these diagnoses were confirmed by autopsy, and how much this incidence of arterial disease exceeds that of a similar age group from the general population)

According to Joslin the prevention of arteriosclerosis is favored by reduction of weight to the normal level Advice that we heartily accept But we are incapable of finding any sound basis for the statements that "The avoidance of a high fat, low carbohydrate diet is another preventive influence I suspect that the development of arteriosclerosis in our diabetics has been caused largely because the carbohydrate in the diet was lowered and the fat increased out of all proportion Prior to weighed diets this resulted in coma but with under-nutrition and insulin, patients avoid coma and live long enough to show the more subtle effect of the high fat diet, namely atheromatosis" To support these sweeping statements Joslin refers to the record of a patient reported by a colleague This mild diabetic who died at the age of fifty-eight had lived on a diet "low in carbohydrate with an excess of fat" During the last five years of his life his weight rose from 97½ pounds to 174 pounds The autopsy disclosed severe vascular disease throughout the body Can Joslin who has taught all of us the importance of keeping down the body weight of the

diabetic, seriously expect us to believe that this patient who gained 76½ pounds in five years became arteriosclerotic because the fat in his diet irritated his blood vessels. 'Would the great advocate of undernutrition have us forget that the glaring fault in this patient's diet was its excess of calories?'

It is unfortunate that Joslin's paper does not contain a tabulation of the level of blood fats of patients alleged to be harmed by an excess of fat in the diet, for it is well known that the untreated or improperly treated diabetic often shows a marked lipemia, and all agree that its decline is excellent evidence that a proper diet has been prescribed.

Some years ago Marsh (2) and Waller showed that diabetic lipemia was rapidly reduced by the high fat diets used in this clinic. In their summary they wrote, "It is certainly very strong evidence that the prevalent assumption which postulates that diabetic hyperlipidemia is dependent on the excessive ingestion of fat is unwarranted." A summary of some of their data is reproduced in Table I.

that the lipemia present in a group of patients was dependent upon the calories of the diet and that it was uninfluenced by the dietary fat.

The important facts taken from the record of one such patient will serve as an example. A young man who had been moderately obese for many years came to the hospital for the treatment of xanthomata. While still on an uncontrolled diet two determinations of his blood lipids gave the following readings: Total lipids 2.275 and 2.215 grams per cent, and cholesterol 0.323 and 0.316 grams per cent. The serum was creamy in appearance. Further examination showed that he was diabetic. He was desugarized and then given a series of diets containing increasing amounts of carbohydrate. During this period of thirty-five days he lost twenty-nine pounds due to the low energy values of the diets. The xanthomata began to involute shortly after the diabetic diets were begun and had disappeared before the end of this first period. Throughout the second period of thirty days his diet consisted of protein 55 grams, fat 210 grams and carb.

neither gained nor lost weight. After forty-five days on this diet, the blood fats were as follows: Total lipids 1.175 grams per hundred and cholesterol 0.225 grams per hundred. The important figures for our present purpose are brought together in Table 2. The table makes it clear that the

cept in so far as it was a source of calories

### CONCLUSIONS

Some clinicians believe that diabetic arteriosclerosis bears a casual relationship to the patient's diet. At present

TABLE 2—THE RELATION BETWEEN CALORIES AND BLOOD FATS

Diet				Blood Fats		Remarks
Protein	Fat	Carbo- hydrate	Calories	Total Lipids	Choles- terol	
				Mgs Per Cent	Mgs Per Cent	
55	210	300	3310	2416	400	Gain of 8 pounds in 30 days Glycosuria
55	210	100	2510	1175	225	Weight constant Urine normal

marked lipemia which resulted from a high fat diet excessive in calories, was reduced to half its former value in forty-five days by a second diet containing the same amount of fat but whose calories had been lowered to the maintenance level. It is evident that, in this patient, fat was without effect upon the lipemia ex-

there is insufficient evidence to either prove or disprove this hypothesis.

If such a relationship exists, the fault lies in excess of calories. The vascular disease is not caused by the metabolic products of fat and the latter may take part in the production of arteriosclerosis only in so far as it is a source of calories.

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# Some of the Difficulties in the Diagnosis of Cancer of the Internal Organs\*

By JOHN M. SWAN, M.D., F.A.C.P., *Rochester, New York*

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**I**N 1927, 14,254 people died of cancer in the State of New York. Of these deaths, 7,448 or 52.2 per cent occurred in the City of New York, and 6,806 or 47.8 per cent occurred in the remainder of the State. There were 4,790 cases of death from cancer of the stomach and liver, or 33.6 per cent of all the deaths from cancer. Of these deaths 2,547 occurred in New York City, or 53.1 per cent, and 2,243 occurred in the remainder of the state, 46.9 per cent. There were 2,404 deaths from cancer of the peritoneum, intestines and rectum or 16.8 per cent of all the cancer deaths. Of these 1,226 occurred in New York City and 1,178 in the remainder of the State.

City and in the State outside of New York City, are almost identical.

In its attack on the cancer problem, the American Society for the Control of Cancer has adopted the slogan, 'In Early Treatment Lies the Hope of Cure.' Early treatment cannot be undertaken unless early diagnosis is made. Cancer of the various parts of the digestive tract and other internal organs is not easy to diagnose in its early stages. The object of this paper is to point out some of the difficulties in early diagnosis. It is sometimes necessary, especially for a consultant, to give an opinion on the basis of a few facts.

morning expectoration. Glucose had been found in his urine at some previous time and he had a chronic nasopharyngitis. The man was a hearty eater and apparently ate more carbohydrate than proteid food. Upon physical examination it was found that he had a moderate amount of pulmonary emphysema, a slightly increased area of cardiac dulness (oblique diameter 17 cm) a weak heart muscle, a palpable liver edge, and a low blood pressure (systolic 109 mm). He was then twelve pounds overweight and there was a trace of glucose in the urine. During the following ten months, he lost eighteen pounds more so that he was about six pounds under weight. He was not, however, complaining of symptoms, and had reported for physical examination only. The liver edge was palpable on deep inspiration but there were no areas of tenderness in the abdomen. In the following years he had frequent attacks of general muscular pain, fever and constipation, with occasional other manifestations like herpes labialis and glycosuria. During this period his weight fluctuated so that at one time he had gained twenty-one pounds over his lowest weight. He was thought to be a man having a chronic nasopharyngitis with periodic exacerbations, and possibly a subacute cholecystitis. In September, 1917, he began to complain of his usual symptoms with the addition of a good deal of abdominal pain, which he ascribed to eating corn. He also said he was "low spirited and felt mean." He was seen at 8 P. M. when he acted as though he had been drinking, his temperature was 99 de-

grees, pulse 100, respirations 24. The tongue was coated, the abdomen was distended, there was epigastric tenderness and the liver edge was palpable. He was thought to be undergoing one of his usual attacks of acute exacerbation of his chronic nasopharyngeal disease with an added digestive disturbance. He did not do well and a surgeon who saw him thought he had carcinoma. He was operated upon and a diffuse inflammatory condition involving the surface of the liver with omental adhesions overlying a carcinoma of the liver was found. The primary source was unknown. The rectum was negative, the stools showed no occult blood and the X-ray pictures suggested no lesion in the stomach or the bowel. He died a few days after the operation. No autopsy was allowed.

The question arises whether this patient, when first seen in 1913, having lost fourteen pounds in weight having a history of glycosuria, and a palpable liver edge had a beginning carcinoma, perhaps of the pancreas. If so the periodic attacks of fever, general muscular pain and constipation that he had during the four following years might be due to the extension of the growth and not to acute exacerbations of a chronic nasopharyngitis. If so, would operation at that time have resulted in complete removal of the growth and cure? The finding of malignant disease of the liver in the 1917 attack was a complete surprise to me. The attack seemed in no way to differ from previous attacks, except for the suggestion of alcoholic intoxication on the first evening of its development.

If we are to prevent cancer of the liver and pancreas, we must look for a way to decide whether to operate when the indications are as indefinite as loss of weight, glycosuria and a palpable liver edge. Very likely a history of typhoid fever, followed by a palpable liver edge, occasional glycosuria, and sharp loss of weight ought to warrant a search for a beginning carcinoma. At all events we ought to keep constantly in mind the probability that all individuals beyond the age of forty-five may have beginning carcinoma.

In October, 1913, I saw a man aged forty-nine years who had complained

where fairly firm and deep pressure brought out pain. The spleen edge was indistinctly palpable and slightly tender. The stomach tympany extended from the sixth rib to the eighth rib. The greater curvature of the stomach was 4 cm. above the umbilicus. There was a moderate amount of cyanosis in the recumbent posture. A blood count gave the following results: Erythrocytes, 4,460,000, leukocytes, 8,880, hemoglobin, 89% (Sahli), color index, 0.99. Differential count: polymorphonuclear neutrophils, 70.0% = 6,216, lymphocytes, 22.9%, large mononuclears, 4.8%, eosinophiles, 2.4%.



pronounced anemia Twelve days after this opinion was written, the patient had an attack of abdominal pain and diarrhea, with fever to 103 degrees and localized tenderness in the gall bladder region Two days later the man was operated upon There was a moderate amount of ascites, the liver was nodular and hard The gall bladder was enlarged and was bound down beneath the liver well over to the right side, its surface was nodular There were two hard nodules in the head of the pancreas The histological examination has been lost The operating surgeon felt sure that the disease was malignant

A man, aged forty-eight years, complained of regurgitation of food and vomiting He had had stomach trouble for ten years He began by regurgitating his food, at first the material was not sour but later it became sour About six years later he began to complain of nausea but at that time there was no vomiting About six months before he was first seen he began to vomit, at first the vomitus was watery but later it contained food, very little changed in appearance At first the attacks of vomiting were not frequent, but during the last month or two he had vomited more frequently, sometimes every day, sometimes two or three times a week He had not vomited blood He complained of distress and griping pain in the stomach, gas and borborygmus Sometimes he had diarrhea He had an attack with fever about a month before I saw him in which his bowels moved every hour, the stools, which were greenish black in color, contained mucus,

but no blood There was a bad taste in the mouth, gas in the stomach and intestines, and often sharp cramps in the thighs and the legs at night His appetite was entirely lost He thought he had lost twenty pounds in weight in the previous month On physical examination extensive dental caries with recession of the gums was found

The following is an abstract of the abdominal examination "The abdomen measures 69.5 cm in circumference The abdomen is retracted There is a distinct pulsation in the line of the abdominal aorta The left side of the upper segment seems a little fuller than the right The inguinal lymphnodes are palpable on both sides There is some tenderness on deep pressure in the left upper quadrant There are no tumors In the midline 2.5 cm above the umbilicus there is a distinct area of tenderness Stomach The stomach tympany measures 21 x 12.5 cm In the left midclavicular line the stomach tympany extends from the sixth interspace to 4 cm below the costal margin The greater curvature of the stomach is at the umbilicus Examination of the pyloric end of the stomach for tumor is negative After inflation the stomach tympany measures 23.5 x 14.5 cm In the left midclavicular line the stomach tympany extends from the sixth rib to 4 cm below the costal margin The greater curvature of the stomach is 1.5 cm below the umbilicus There is a good deal of borborygmus The patient complains of a sensation of smarting and burning and while the gas was in his stomach he vomited a moderate quantity of white frothy material"

I gave the following opinion "I believe the case to be one of simple dilation of the stomach. You will see by the record that I inflated his stomach and determined a considerable amount of dilation with a greater curvature well below the umbilicus. I do not believe the dilation is dependent upon pyloric obstruction. I doubt very much if there is an ulcer, although, of course, the possibility of an ulcer of the duodenum must be kept in mind." I did not think the case was one of cancer of the stomach. Four days later gastrectomy was done and the pyloric third of the stomach was removed. There was a round mass as large as a golf ball connected with greater curvature of the stomach presenting ventrally. The wall of the stomach was thickened. There were numerous enlarged lymph nodes along both the greater and the lesser curvatures of the stomach. On opening the removed portion of the stomach an infiltrating mass was seen involving the entire wall of the organ, resembling enlarged rugae. This mass

dietary habits complicated by mouth infection that I did not suggest an X-ray examination. The possibility of carcinoma was evidently considered, as indicated by the note about tumor. The man went from me to the surgeon who operated on him who felt that there was a mass in the stomach region and recommended X-ray examination, which demonstrated the mass. The case illustrates the importance of keeping the possibility of carcinoma in mind in spite of a symptomatology which is not characteristic of malignant disease. It should be pointed out that this patient showed no evidence of gastric bleeding and that no mass was felt. Nevertheless, we must always be suspicious of carcinoma in cases of persistent indigestion. If we wait for the classical symptom complex, indigestion, loss of weight, anemia, and tumor we shall be too late to accomplish cure by any method whatever. In any case of persistent indigestion X-ray study of the gastro-intestinal tract is demanded, particularly a fluoroscopic

was negative, and that there was pus in the urine I sent her for a pelvic examination. This showed a "Fibroid tumor the size of a grape fruit causing pressure symptoms of the bladder." The gynecologist recommended hysterectomy but the patient did not wish to follow the advice and, since she had passed the menopause, I did not urge her to have operative interference. Five months later she was seen again, complaining of pain low down in the back and soreness on the anterior surfaces of the thighs. She also complained of gas in the stomach and on six occasions she had vomited about five hours after her supper. The vomitus consisted of mucus and undigested food. There was no hematemesis and no coffee ground vomiting. She had lost no more weight but now I could determine, on examination of the abdomen, that it was uniformly distended, with tenderness in the right lower quadrant and in the epigastrium. There was a small, hard tumor in the hypogastric region, deep down. In the right upper quadrant to the right of the median line and above the umbilicus there was a mass, hard, not tender. On deep respiration the lower border of the liver seemed to cover it. I ordered a cathartic for the patient and asked her to bring me a twenty-four hour specimen of urine. After taking a part of the cathartic ordered she vomited about a quart of mucus with a good deal of retching. The vomitus did not contain blood and did not resemble coffee grounds. The patient brought 20 c c of urine which she said was her entire twenty-four hour output. I

thought that the fibroid tumor had become jammed in the pelvic inlet, that the mass in the right lumbar region was a hydronephrosis, and that the vomiting was due to an attempt on the part of the gastric mucosa to excrete urea. The surgical consultant thought the disease was malignant and that the mass in the lumbar region was a metastatic growth. At operation a "large malignant tumor filling the pelvis, fixed about the pelvic brim, involving by direct extension both ureters (was found)." Retroperitoneal metastases were present especially in right side chain. Mass discovered in right upper quadrant is large metastasis matted in region of right kidney." The patient died several days after the operation of suppression of urine. No autopsy was allowed.

The question of uterine myomata is one of major importance and it is a question upon which the internist is frequently obliged to express an opinion. It seems to me that the advice of Crossen is the most conservative and offers the best prospect for prolonged life and freedom from illness for the patient. "A myoma of the uterus which has reached a size to be appreciated clinically is a more serious affection than is generally supposed. A considerable proportion of patients develop fatal local conditions, another considerable proportion of the patients develop serious visceral degenerations, and a large proportion finally pass into a condition of chronic suffering and invalidism." (*Diseases of Women* Ed vi 596)

In June, 1914, I saw a woman aged sixty-three years. In October, 1912, her left breast had been amputated



nodule in the scar over the right deltoid muscle, I feel that the consolidation at the base of the left lung is due to extension of the carcinoma to the lung, although I think it curious that there is no more pain. The physical signs at the base of the right lung I take to be the result of old pleurisy, but it may be carcinomatous. The emphysema at the apices of the lungs is compensatory. On account of the high blood pressure, the contracted pupils and the occurrence of albumin and casts in the urine, it is just pos-

sible that the whole pulmonary complex is the result of nephritis."

The patient died five days later. An autopsy was obtained which, among other things, proved that the pulmonary symptoms and signs were due to the carcinoma of the pleura, carcinoma of both lungs (bases) and pulmonary emphysema (upper lobes). The kidneys were the seat of a chronic parenchymatous nephritis. There were 500 cc of blood-stained fluid in the left pleural cavity.



ture occurs externally, through the adventitia, and since by reason of hemodynamic stress and anatomical structure, the majority of dissecting aneurysms involve the first portion of the aorta, hemorrhage into the pericardium is by far the most frequent terminal event

In approximately one case out of six there occurs the remarkable phenomenon of rupture of the new channel internally, into the lumen of the aorta, so that the blood from the false passage regains its normal pathway. In this event, the walls of the dissected area become lined with a new intima, may be further strengthened by connective tissue proliferation, and the result is a 'healed dissecting aneurysm (9)'. In consequence, the patient may live, even without consciousness of a circulatory defect, for many years.

Dissecting aneurysm, in short, forms a "tube within a tube" which may extend the length of the aorta and involve the whole or part of its circumference. In the process of dissection, the arterial trunks springing from the aorta may be compressed or occluded, and not uncommonly the smaller arteries such as the intercostals, are entirely torn away from their sites of origin.

#### ETIOLOGY

Arteriosclerosis furnishes the common substratum for the primary intimal rupture; the immediate cause being sudden physical strain, trauma, excitement, all factors which induce circulatory stress. And it is not the grossly calcified plaque, but the hya-

line fibroid" lesion of Adam (10), at once brittle and closely connected with the media, which is peculiarly involved. Therefore, while dissecting aneurysm is largely a lesion of later adult life, it is a commentary on the development of aortic atheromata that many ruptures have occurred in the fourth, and even at the end of the third, decades.

Infectious processes involving the aortic tunics undoubtedly play a role in younger people, but syphilis, it is important to note, is a relatively insignificant factor. Thus von Schnurbein (11), in 91 carefully analyzed cases, found only one instance of definite syphilitic involvement and Loeschke's (12) small series of cases is only an exception to the general rule. The best explanation is that the characteristic syphilitic mesaortitis disrupts the orderly arrangement of the layers and makes for local sacculation rather than wide dissection.

In young adults and children, there is an interesting group where coarctation, or stenosis, of the aorta is the factor which leads to dilatation and rupture of the first portion of the aorta.

In some instances, the anatomic changes in the aorta are slight or absent.

#### CLINICAL CLASSIFICATION

On the basis of their clinical features and course it is possible to divide patients with dissecting aneurysm of the aorta into three groups.

1. Those in whom the rupture of the intima, dissection of the media and perforation of the adventitia take place within a few seconds or min-

utes, and death is sudden and without previous warning

2 Those in whom the process goes on more slowly, the stages are separated by varying intervals of time, and symptoms and signs of disease arise which are susceptible of observation, analysis, and diagnosis. In this group, the intimal tear may cause pain and collapse, a period of freedom from symptoms may ensue, and then some element of strain brings about the terminal phenomena, days, weeks, or months after the prodromata

3 The group of those in whom the dissected channel reenters the normal passage, and "healing" takes place. Obliteration of the false passage by

invariant features appearing in numbers of carefully observed patients result in a reasonably characteristic picture, as may be made clear by a few briefly presented case reports

*Case I (13)* —A man, aged 37 years, stout and plethoric, previously well, in the middle of a heavy meal, fainted. On recovery, he complained of violent abdominal pain and nausea, with pain in the back. The pulse was feeble and irregular, and the abdomen swollen and tense, but not very tender.

Next day, there was severe pain in the loins, radiating to the testicles. The pulse was now full. Clear urine was passed.

On the third and fourth days, there were suppression of urine, drowsiness, twitching, and the appearance of complete left-sided hemiplegia. The right radial pulse was smaller and feebler than the left, but the



the patient was seized, two hours after eating a rather full meal, with intense pain beneath the upper sternum, radiating to the outer side of the left arm, and increased, within an hour, by pain in the lumbar region of the same constancy and intensity.

In the substernal and lumbar pain continued during four days, gradually subsiding and disappearing on the fifth day. Blood pressure remained high, was the same on the two sides, there were no noticeable changes in heart signs, the urine remained clear, there was a slight febrile reaction.

The pulse became irregular and an electrocardiogram showed periods of sinoauricular block and numerous nodal premature beats, but no evidence of coronary artery disease.

Death occurred suddenly on the seventh day after the appearance of Cheyne-Stokes respiration and a terminal rise of blood pressure to 230/160 mm.

There was a dissecting aneurysm extending from the arch to the bifurcation of the aorta with perforation into the mediastinum and left pleural cavity. The dissected channels lined in part with a smooth intima. The aortic cusps were normal, there was no late atheromatous change in the aorta.

**Case 3 (15)**—A man, aged 38 years, usually strong and well developed, with no history of reining in two "green" horses, suddenly felt a sharp, sticking pain in the chest, with headache and nausea immediately following. From this attack he recovered promptly, but next day his horses balked and it took all his strength to control them. Now with greater intensity he felt the pain in the chest, with vomiting, weakness, and loss of power to see clearly for 12 hours.

Pathological findings were made out by a physician who was called, the vomiting ceased on the following day, and the patient could again see and speak. He complained of a strange and uncomfortable sensation in his chest, and 48 hours after onset, he suddenly died.

Necropsy showed a dissecting aneurysm of the aorta extending from above the level of the left common carotid, and

a rupture into the pericardial sac. In this man the aortic wall appeared healthy, but there was a slight degree of stenosis of the aortic valve and the left ventricle was hypertrophied.

**Case 4 (16)**—A woman, aged 63 years, suffering from dementia, had been physically robust, accustomed to brisk walks in all sorts of weather, until overtaken by apoplexy, following which, while at rest in bed, she had repeated attacks of pain in the chest diagnosed as angina pectoris.

Following the necropsy, the additional history was obtained that 18 years before the date of death, the patient had been thrown from a sleigh, striking on her head and becoming unconscious, and for two months had been confined to the bed. Three months after the accident, there was an attack of loss of consciousness. Shortly after the psychosis developed, and occasionally she showed mild circulatory weakness.

There was found generalized arteriosclerosis, with an area of hemorrhagic degeneration in the right corpus striatum, and a dissecting aneurysm extending from the arch to the coeliac axis, where through a second rupture the outer channel joined the aortic lumen. The aneurysmal wall was smooth and lined by intima. In the ascending arch there was a small adventitial tear, 1.5 cm in its largest diameter, containing coagulated blood.

**Case 5 (3)**—A man, aged 52 years, was in good health until an attack, after he had eaten breakfast and was starting for work, of syncope, cold sweat, pallor, cyanosis, subnormal temperature, and the disappearance of both radial pulses.

After digitalis, the right pulse returned, while the left arm felt "very heavy." Hemiplegia was absent.

Four hours after the attack, there was severe pain in the heart and in the upper back. The left pulse could now be felt, but there was marked inequality. The right brachial blood pressure was 200/100 mm, the left 100/60. The heart was enlarged to the left, regular, rate 70 beats per minute. Strong spontaneous pain continued in



versus gastrointestinal disease must be weighed. It is worth noting that dissecting aneurysm may be accompanied by a marked leukocytosis.

(3) Among the circulatory changes distinctive of dissecting aneurysm the presence of a harsh, rumbling, or hissing systolic murmur over the heart and great vessels has been recorded. Inequality of the pulses, or their absence in various domains—the arm, one side of the neck, the lower extremities—are important evidence of compression or occlusion. Bilateral blood pressure determinations are helpful under these conditions. The appearance of adventitious enlargements within the thorax, in the neck, or along the abdominal aorta, accessible to palpation or percussion, or revealed by X-ray, have been clues to diagnosis.

(4) Interference with the cerebral blood supply is frequently associated with dissecting aneurysm, and the complete obstructions to carotid circulation which may thus arise may be responsible for encephalomalacia, hemiplegia, and death. Coronary circulation is less often interrupted. Compression of the renal arteries has been seen to precede anuria, and characteristic renal pain. In cases of abdominal distention, with ileus, pressure of the dissecting-aneurysm on the splanchnic nerves has been considered.

Extravasations of blood follow in the path of the damage done by dissecting aneurysm to the aortic wall or the circulation in its branches, and

have produced hemoptysis, hematemesis, and hemorrhage into the intestine. Hemoglobinuria has been found. Gangrene of the foot has followed obstruction to the femoral artery, and paraplegia resulting from meningeal bleeding has been noted as one of the more remote phenomena caused by dissecting aneurysm.

In Goodman's (17) patient, a man of 40 years, who recovered, dyspnea, severe pain in the upper chest which followed unusual physical strain, a left hemothorax, and aneurysmal dilatation of the aorta, with no history or evidence of syphilis, and a negative Wassermann blood test, made up a picture which meets these clinical criteria convincingly.

#### SUMMARY AND CONCLUSIONS

Dissecting aneurysm of the aorta is a remarkable and well known pathological condition, of which over 400 cases are recorded. In only a handful of patients has the disease been recognized during life. This disproportion challenges clinical attention.

Analysis of the clinical features and course shown by patients with dissecting aneurysm yields a syndrome which in certain groups of cases can be considered characteristic. These features are: a sudden onset, usually following strain, pain, which is severe, continuous, and often with significant distribution, anomalies of the circulation, remote effects from disturbances of blood supply in other organs or systems of the body.

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# Ulcerative Endocarditis of the Pulmonic Cusps\*

## Case Report

By EDWARD WELISS, M D , *Philadelphia, Pa*

**L**S, a colored woman of 34, was admitted to the Jefferson Hospital in the service of Dr Thomas McCrae, January 24, 1928

She complained of pain in the right chest, chills, cough and expectoration. The family history was negative. The past history was unimportant. The patient had one son nine years old and had three miscarriages prior to the birth of her son.

The history of the present illness was not quite clear. Apparently it began late at night on January 18, with pain in the right chest posteriorly, but there was some history of two attacks of chills a week or two before this time. The pain in the chest increased the following day. Cough began about January 21. There had been repeated chills since the beginning of the illness.

Physical examination showed a very sick, obese, colored woman, with marked dyspnea. The temperature was 103, pulse 112, and respirations 30. The apex beat was in the fifth interspace almost to the anterior axillary line and left ventricle dullness extended to that point. There was a systolic murmur at the apex which, however, was loudest in the third interspace to the left of the sternum and at that point had a rough quality like a pericardial friction rub. It also was heard in the pulmonic area but not to the right of the sternum. The upper portion of the right lower lobe posteriorly gave evidence of consolidation. There was dullness on percussion and distant tubular

breath sounds with small moist rales. Otherwise, the physical examination showed nothing of importance.

The blood pressure was 190/74, the blood count, hemoglobin 50 per cent, red blood cells 3,100,000, and white blood cells 30,000. The urine showed a cloud of albumin, a large number of white blood cells, many red blood cells and many granular casts. The sputum yielded group IV pneumococcus. The blood Wassermann was negative.

The clinical picture was not definite. It was thought that there was an atypical pneumonia of the right lower lobe complicating a heart lesion. On January 27, three days after admission, the temperature suddenly dropped almost to normal but the pulse remained about 120 and the respirations 28. Physical signs were unchanged over the lungs but the character of the murmur heard over the body of the heart seemed somewhat different in that it was distinctly to and fro with the diastolic element very pronounced. Together with the great disparity in the systolic and diastolic pressures which now were 185 and 60, and a very suggestive collapsing pulse, it seemed that the heart lesion was probably aortic regurgitation.

The urine continued to show albumin, blood and casts, and chemical analysis of the blood, which showed slight nitrogen retention on January 27, showed very marked retention on January 30, the urea-nitrogen was 120 mg and the creatinin 95 mg. The carbon dioxide combining power of the blood was 30.5. The blood culture was negative at the end of 48 hours.

\*From the Department of Medicine, Jefferson Medical College Hospital, Philadelphia.

Following the drop in temperature on January 27, there was apparently slight improvement but soon the patient became drowsy, then stuporous and finally comatose on January 30. The conception of the clinical picture at this time was probable aortic regurgitation, pneumonia (or infarct) of the right base and a complicating acute renal lesion (possibly engrafted upon an older process) leading to uremia.

The patient died on January 31. Autopsy (Dr B L Crawford) revealed a pneumonic area in the middle portion of the right lower lobe posteriorly, chronic nephritis and ulcerative endocarditis of the pulmonic valve. Portions of two cusps were ulcerated but the vegetative lesion had neither the appearance of being very acute nor apparently had it been engrafted upon chronically diseased valve cusps. Smears from the vegetations did not show organisms. Microscopic sections of the vegetations revealed necrotic tissue with groups of polynuclear leukocytes and occasional fibroblasts but no mass of organisms. Only a few gram-positive diplococci were seen in properly stained sections. Postmortem blood culture was negative. The left ventricle was somewhat hypertrophied but otherwise there were no additional lesions of the heart. Microscopic examination of the lung showed a fibrinous pneumonia, and of the kidney an acute exacerbation of chronic glomerular nephritis.

It is difficult to say with certainty what the sequence of events in this case was. Did the pulmonary valve endocarditis complicate the pneumonia or was the period of illness with vague symptomatology preceding the onset of pneumonia caused by endocarditis? In the latter event the pneumonia might be explained on the basis of an embolus from the pulmonic orifice. Unfortunately microscopy did not aid materially in determining the age of the vegetative lesions. It is more than likely, however, that the endocarditis was a complication of the pneumonia. The chronic renal lesion must have been responsible for hypertension and left ventricular hypertrophy, and renal insufficiency seemed responsible for death. The unusual localization of the vegetative endocarditis, the difficulty in determining whether it was primary or secondary, and the fact that it was considered clinically to be aortic regurgitation are the special features of interest in this case.

# Albuminuria and Nephritis Following Injection of Toxin Antitoxin\*

With a Report of Two Cases

By C D MERCER, M D, F A C P, *West Union, Iowa*

**I**MMUNIZATION of school children against diphtheria with Toxin-Antitoxin has been undertaken on a wholesale scale in Iowa. The physicians of our little city were asked to give these injections, working in relays at the school building, using a stock serum manufactured by a well known firm, and supplied by the State Board of Health. Having fresh in my mind an article by Gersterley (1) reporting a sudden death from nephritis in a child who had been immunized, I asked that the children be sent to their own physician where a suitable history could be taken and physical examination made.

One hundred twenty five children between the ages of six and twenty appeared for immunization. Thirteen or 10% had albuminuria without other symptoms of nephritis. Hess (2) states that 10% of boys and 20% of girls show this condition during stages of their development. More than 50% of the children in this group had enlarged tonsils and adenoids. The children were given 1 cc of the stock serum at seven day intervals for three

doses. After the third injection 27 or 20% had albuminuria.

## Case Reports

*L R*, aged 7, with enlarged tonsils and adenoids, anemic and poorly nourished, was examined Dec 5, 1927 and found to be free from albumin. He received three injections of the T-A mixture at seven day intervals, receiving the last injection Dec 19, 1927. Two weeks later he was admitted to the hospital with the following symptoms: Generalized edema of his whole body. Hemoglobin 70%, RBC 3,200,000, WBC 5000. Blood pressure 115/80. Urine—Sp Gr 1020, albumin 4 plus, sugar negative, many hyaline and granular casts. PSP 40. Non-protein-nitrogen 46.4 mgs per 100 cc blood. Wassermann negative. Patient was put in bed, kept warm and given an O'Hare (3) nephritic diet. Intake of fluids restricted to output. On Feb 6, 1928, 2500 cc fluid was withdrawn from abdomen. Edema, ascites and hydrothorax with albumin and casts in urine continued until Feb 12 when symptoms began to clear up. On Feb 17 there was no edema, albumin or casts present. Albumin without edema re-appeared Feb 26 and continued until March 13. On March 30 patient left the hospital free from edema and urinary symptoms. PSP 75. Patient has remained free from symptoms up to the present time July 1, 1928.

*R C* was admitted to the hospital Jan 18, 1927 with a diagnosis of chronic nephritis. Age 20. Had scarlet fever at age 8 and has had trouble with kidneys most of life. Had a mastoid infection at

\*From the West Union Community Hospital.

age of 16 which was not operated but allowed to go on to necrosis of bone This discharged for several years but finally healed Physical findings Hemoglobin 60%, RBC 3,850,000, WBC 6000 Urine Sp Gr 1015, albumin 2 plus, sugar negative, showers of granular casts Creatinin, 1 mgs per 100 cc blood, Urea nitrogen, 15 mgs per 100 cc blood PSP 35 Wassermann negative Blood Pressure 260/120 Patient was given routine treatment for thirty six days and left the hospital with a negative urine Returned in seven days with a very severe Vincent's Angina Recovered after two weeks and again left the hospital with a negative urine Patient remained free from symptoms during the summer and gained sixteen pounds in weight In September she was given three injections of a stock T-A mixture at seven day intervals Within a few days after the last injection albumin re-appeared in the urine She had another attack of Vincent's Angina in December and was admitted to the hospital again April 5, 1928, very ill Sp Gr of urine 1005, albumin four plus, granular and hyaline casts and some pus PSP 30 Creatinin, 5 mgs per 100 cc blood Urea nitrogen, 27 mgs per 100 cc blood Blood pressure 260/160 Hemoglobin 60%, RBC 3,200,000, WBC 20,000 Patient died April 18, 1928 No autopsy could be obtained

Rhoades (4) after a study of the protective value of stock preparations

on nurses in Cook County Hospital, emphasizes the necessity that the preparations should be carefully controlled

Experience in this group of children would seem to show that either more refinements are needed in the manufacture of the preparations or the profession should also study the toxic effects more closely before it is given in a wholesale way, or both

### SUMMARY

1 A great many apparently healthy children have albuminuria

2 Administration of T-A doubled that percentage in 125 school children

3 Urine examinations should be made in all cases before immunization

4 Until the manufacturers furnish a better preparation it should be given with caution

5 Potential nephritics, patients with remission nephritis and children with throat trouble should not be given stock serum without careful study

6 Toxin-Antitoxin is not "A harmless preparation" and should not be given school children in a haphazard way

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# Report of a Case of Complete Heart-block with Autopsy Findings

## Syphilitic Myocarditis and Aortitis

By WALTER J. WILSON, *Detroit, Michigan*

**F.** A B, physician, aged 44, married, parent of two apparently healthy children, ten and five years of age respectively

*Parental History* Father living and well at 70 years, mother died at 68 years of carcinoma of the rectum and an associated auricular fibrillation and cerebral thrombosis. There is a history of two brothers living and well.

*Personal History* Army service. At one time had a sore tongue, had a peculiar sensation in the heart after an eighteen-mile walk and had a systolic blood-pressure of 180 while in the service. Military discharge papers call attention to a peculiar heart-sound.

*Past History* There has been no previous illness, except an attack of gonorrhoea in earlier adult life, also an attack of acute rheumatic fever about four years ago. In 1921 an X-ray picture was thought to show a knob on the aorta. In 1924 a heart murmur developed. In 1925 he entered a sanitarium on account of stiffness of the joints. Each time that he took a bath, he had an attack of syncope. When seen by me December 1, 1925, examination showed cardiac enlargement, enlargement of the aortic area, muffled first sound and the second aortic sound was replaced by a diastolic murmur. The blood Wassermann at this time was reported XXXX.

*Recent History* When seen again August 3, 1927, the blood-pressure was 230/80, pulse rate 48, heart rate 46 with one premature beat per minute. X-ray examination showed marked aortic enlargement and a duck-shaped heart. The electrocardiographic record showed complete heart-

block, two beats of the auricle to one of the ventricle with widening of the RS interval and signs of left bundle-branch block, together with a number of premature systoles. The patient was at this time sent to St. Mary's Hospital for observation. From then on, the pulse-rate was at various times 30 to 52. He had had during a few weeks previously different heart attacks with loss of control of the lower extremities. At times he lost control of his automobile, driving it into the ditch, however, he did not lose consciousness. About Sept 1, 1927, two blood Wassermanns at different laboratories, were XXXX. The patient died on Oct 9, 1927. Previous to death, he had Cheyne-Stokes respiration.

*Physical Examination* Sept 10, as on Hospital chart. White adult male, lying quietly in bed with a back-rest and in no apparent pain, although there is a look of apprehension on his face. *Head, eyes, ears and nose*—negative. Mucous membrane. Fair color. Teeth. Good condition. Neck. No palpable glands, no enlargement of the thyroid. Chest. Well developed and well-nourished, moves well and equally on respiration. Reasonance throughout, breath sounds vesicular throughout, no rales heard.

*Heart* Apex beat not seen, on palpation the apex beat is tapping in character. The heart sounds are of poor quality, a double murmur being heard over the whole precordium but more marked in the aortic area. There is a systolic murmur in the mitral area. The blood pressure is 180/20. The radial vessels are not thickened. The rate is 51. The pulse rises quickly and is not maintained but falls quickly. The

pulse on the right side is stronger than that on the left, which seems to be slightly retarded. Owing to soreness of the left arm, the blood pressure was taken only in the right arm.

*Abdomen* Well-developed, well-nourished, moves freely on respiration, liver, spleen and kidneys are not palpable. No masses were felt, no areas of tenderness.

*GU* Negative

Extremities Negative

Reflexes Present, equal, active

Laboratory Findings Sept 11, 1927

Urinalysis Color, amber, clear, reaction acid, specific gravity 1.022, no albumin, no sugar, an occasional WBC

Blood Wassermann XXXX positive

Blood-count WBC—800, polys 71%, small lymphocytes 27%, abnormal 1%

September 22, 1927

Blood-count Hemoglobin 80%, index 1.02, RBC 3,900,000, WBC 9,400, polys 76%, small lymphocytes 33%, abnormal 1%

*Therapeutics* Barium chloride was used in doses of 1/15 gr three times a day, without any apparent effect on the heart-rate. Sodium iodide was introduced intravenously throughout the time of observation, fifteen grains usually being given. On one occasion, when introducing 31 grains rather slowly, short periods of cardiac asystole were noted and thereafter, the dose used was never above fifteen grains. Atropine sulphate in dosage of 1/100 grains was given but simply seemed to distress the patient in general, without any change in the heart-rate. Mercury salicylate, dosage one grain, was given once a week.

An autopsy was performed by Dr. Jas E. Davis on October 10, 1927. The report follows:

*Note* Positive findings only recorded

*Subject* Well-nourished, fairly stout body, florid complexion

*Thoracic Cavity* The heart is enlarged, the left ventricular thickness 3 cm. Weight of the heart with aorta, 940 grams. The papillary muscles are enlarged and sclerosed. The chordae tendinae are enlarged

and fused. The mitral valve is thickened and sclerosed, physiologic approximation is doubtful as the valve assumes a circular and fixed position when natural approximation is afforded. The right ventricular cavity is small, the wall being 1 cm thick. The tricuspid valves are normal. The pulmonary parts are negative. The aortic valve opening is large, the leaflets have a low attachment and the middle leaf is greatly increased in length to approximately 4 cm, the leaflet is thickened and extensively calcified. The coronary vessels are enlarged, their walls stiffened. The atrial walls show some fibrosis and thickening and the area of Keith and Flack is definitely sacculated—circumference 13.5 cm. The distal aorta has a circumference of 5.5 cm. There is a diffuse atheromatous degeneration, which extends up the larger neck vessels with a marked lesser degree of involvement.

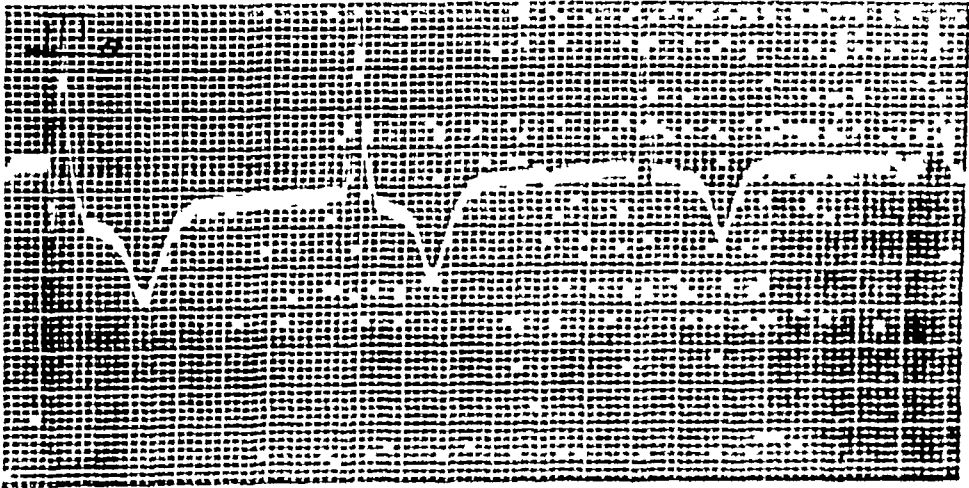
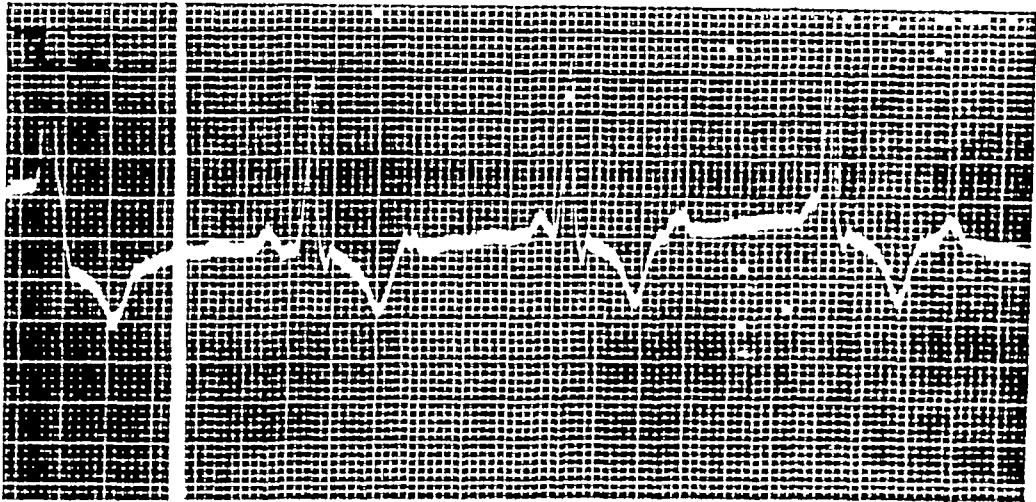
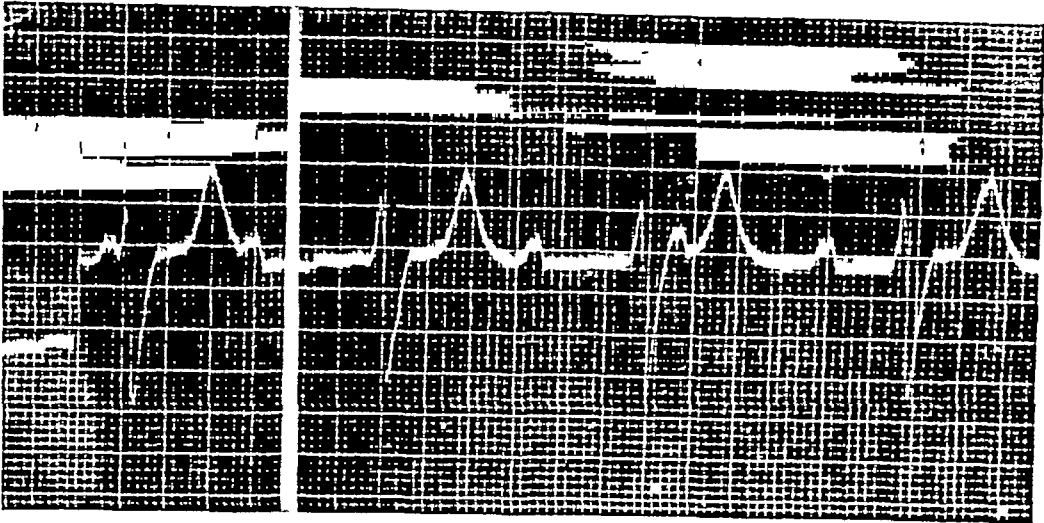
*Abdominal Cavity* The spleen is enlarged and fibrosed—weight 310 grams. The kidneys are of enormous size, show slight cloudy swelling, early atrophy, arteriosclerosis and sclerosis of the apices of the pyramids, there is an increase of pelvic fat. One kidney weighs 180 grams, the other 190 grams.

#### Microscopic Examination

Microscopic sections were taken as follows:

- 1 section from lower part of thoracic aorta
- 1 section from area of the pacemaker node of Keith and Flack
- 1 section from left ventricle
- 1 section from papillary muscle, left ventricle
- 1 section from proximal aorta
- 1 section from carotid artery
- 1 section from coronary artery in the right ventricle
- 1 section from kidney, including cortical cyst
- 1 section from each kidney
- 1 section from splenic artery

*Microscopic Report* Arterial Wall Exhibits a very marked sclerosis, particularly of the adventitial vessels together with some round-cell infiltration in the adven-



titia There is marked degeneration of the elastica, the intimal margin is irregular and frayed. Another section of the artery shows small round cell infiltration on the intimal surface and fatty degeneration. Another section (artery) exhibits marked calcification and there is early myxomatous degeneration of the connective tissue. Still another section of artery shows masses of lymphocytes infiltrated about adventitial vessels, also degenerating areas in the intima and media with repair tissue and small round cell infiltration in these areas, the intima is irregularly piled up and markedly degenerated.

*Heart Muscle* Shows patchy sclerosis and small round cell infiltration on the epicardial surface and there is an epicardial vessel with a greatly thickened intima. There is an infiltration of small round cells in the interstitial tissue. Another section of heart shows degenerative changes, irregular hypertrophy, large areas of interstitial tissue increase. Still another section shows an area on the endocardial surface diffusely infiltrated with small round cells, partly degenerated and extending up to the valve portion, there are numerous patches in this section in the middle of the heart muscle, showing small round cell infiltration and productive connective change.

*Kidney* The vessels exhibit sclerosis and some vacuole production. The kidney capillaries are congested and the kidney capsule is thickened and adherent. There are patchy areas of old parenchymatous degeneration. In another section the arterio-

sclerosis is extremely marked, there is perivascular small round cell infiltration and there are some cysts in the corticula portion as well as in the pyramidal portion.

*Spleen* Shows marked congestion and atrophy of stroma.

*Specific stain (Levaditi)* for *Spirocheta pallida* Positive Spirochetes were found in the inter-ventricular muscle septum just below the base of the aortic valve, cutting in at right angles in the long diameter of the heart.

#### Diagnosis

- (1) Syphilitic myocarditis and arteritis
- (2) Syphilitic valvular endocarditis
- (3) Sclerosis of pathway tissues of His bundle conduction stem

*Comment* The correlation of data in this case gives an agreement in all details. The alignment of these details being as follows:

- (1) Repeatedly positive blood Wassermanns
- (2) Typical clinical cardio-vascular pathology, with extension from the aortic valve by the interventricular septum so as to involve particularly the stem of the His bundle.
- (3) Descensus of segment attachment of the aortic valve
- (4) Classical structural changes in the large vessels, vasa vasorum and myocardium
- (5) Presence of *spirocheta pallida* in the tissue

# Scarlet Fever\*

By A R DOCHEZ, M D , *New York City*

I WANT to talk to you about certain questions related to the pathogenesis of scarlet fever. As you know, this disease has always been of extraordinary interest. All you have to do to see how perplexing it has been is to consider the history of its epidemiology. At times it appears as a devastating, plague-like infection, decimating whole communities. There are histories of epidemics on record where the case fatality rate has been over 30 per cent. A number of years later it subsides into a fairly mild infection. In this country today the case fatality rate in many localities is 1 per cent. That condition of affairs exists over a large part of the world, but it is not true throughout the entire region of its incidence. In Russia, for instance, and in some of the southeastern countries of Europe the case fatality rate is still high in certain localities. In China, especially among the Chinese, it can assume a plague-like character. It wipes out whole families and it has always been very perplexing to understand how an organism could vary so much in its virulence in relatively short

periods of time. There are those who believed that racial immunity has risen to such a point that epidemics with high case fatality rates are unlikely ever to occur again. However that may be, we still have to consider the threat it offers and devote our time and attention to the study of this disease.

Considerable progress has been made over a period of many years. It began long ago in Austria, and has been carried forward in Russia and other places. I will not leave scarlet fever before calling your attention to the hypotheses of recent years, and certain modifications of these hypotheses which are in course of development today.

As you know the clinical manifestations of scarlet fever present many interesting problems. In the first place, there is a local infection of the throat, more or less severe. It may be simple swelling and edema, with slight exudate, or it may develop to an extensive necrosis, with sloughing. This inflamed condition of the throat goes on for a short time and then there appears a generalized toxic eruption of severe character. This lasts for a varying time, perhaps two days, perhaps six days, and then disappears. With the disappearance of the rash the average mild case without complications shows in

\*Informal address as part of a Symposium on Infectious Diseases at the Twelfth Annual Clinical Meeting of The American College of Physicians, New Orleans, La., March 7, 1928.

mediate improvement in the general condition, the fever subsides and the patient feels well. Accompanying this, especially toward the end of this phase, or even after this phase has subsided, there appear certain septic complications. These are, as a rule, simple extensions of the local condition in the throat. The condition may extend into the respiratory tract from the tonsils, into the regional lymph glands, and from the lymph glands into the tissues of the neck, where it may produce a septic thrombosis of the veins, and from there an infection of the blood takes place and a true septicemia develops. It may establish metastatic foci in other regions, the usual place being in the joints. The septic foci run a varied course. They sometimes disappear quickly and sometime continue for weeks, leading to much difficulty.

Later on in certain cases there may appear quite a different group of phenomena the nature of which we cannot say is understood today. The most significant of these are the changes which take place in the kidney and those which take place in the heart. In the kidney one gets an acute glomerular nephritis, which may reach a considerable degree of severity and subside, or it may continue for a long time. The subsequent course of these nephritides is not entirely clear, but there are many in which undoubtedly complete recovery takes place. The significance of this process to the future of the kidney is not clear. Much work is being done today in an attempt to throw light on this and determine what changes are produced in the kidney

and in what way they can lead to a continuous and progressive disease.

Regarding the changes in the heart there has been much discussion. You have all heard of scarlatinal rheumatism. This appears during the second or third week of scarlet fever, complicated by a mild arthritis and cardiac changes that occur in acute rheumatic fever. There has been some doubt as to the etiology of this type of rheumatism. The older observers were inclined to believe that there existed in the throat a specific virus, that this was activated by the virus of scarlet fever, and that following the scarlet fever the patient had typical rheumatic fever. Another view, receiving more support today, is that this rheumatism and cardiac disease are part of scarlet fever. That is why I say that this disease presents such extraordinarily interesting questions from the standpoint of general infection and pathology of the infectious process. It is a difficult problem to discuss, and I do not wish to give too much time to it. I do want to say enough to show how points of view are changing in regard to the nature of the infectious process in scarlet fever.

You may remember that scarlet fever has been likened to diphtheria, more particularly recently but this idea is not new. It was emphasized by Berge as early as 1895, and also by a Russian investigator who studied scarlet fever in Russia in 1903 and 1908. More recently a very striking analogy between scarlet fever and diphtheria was drawn by Mair in England. The most definite thing he brought out was an explanation of th-

Schultz-Carlton test If the test were positive it was found that if the serum was injected into a patient with scarlet fever the area at the site of this injection was blanched. The previous explanation given for this was that something was lacking in the serum. Mair studied an individual before, during and after scarlet fever. He found that before scarlet fever the blanching substance was absent, and was also absent during the acute attack, but that during convalescence the serum had the power of blanching the skin. Mair deduced from this that the blanching substance is a specific immune body which develops during the attack, neutralized the circulating toxin and causes the rash to disappear. He was prophetic at that time and said that if an antiserum was ever discovered it would possess the power of blanching the skin during the disease. The analogy to diphtheria has been in the minds of many for a long time. However, it has been made much closer in recent years by the development of the serum that in the first instance appeared to be an antitoxin like diphtheria antitoxin, and by the Dick reaction, which appeared to bear a similar relationship to scarlet fever that the Schick reaction bears to diphtheria. This has been much emphasized in the last two or three years. At first a so-called antitoxic serum was developed, by the injection of horses with the living organism that functioned in the body and produced an antitoxic serum. In this serum was injected intracutaneously in patients with scarlet fever during the stage of active rash, after twenty-four hours the rash disappeared at the injected site and did not re-

appear. When injected into patients intramuscularly in larger amounts within thirty six hours, there was an amelioration of all the symptoms. Further studies showed that the toxic substance circulates in the blood of patients with scarlet fever. Injections of the serum causes the toxic substance to disappear from the blood and the patient's serum acquires the power to blanch the rash in an active case of scarlet fever.

In addition to these observations Dr and Mrs Dick have shown that the streptococcus of scarlet fever produces a substance which gives a specific reaction in the skin. Studies of the nature of this reaction seem to indicate that it is similar to the Schick reaction in diphtheria. If normal individuals are tested to the reacting substance there is a variation in susceptibility. A certain proportion are positive and a certain proportion negative. As life goes on the period of greater susceptibility to scarlet fever is past. As this takes place the incidence of positive reaction diminishes and the disappearance of the reaction is interpreted as indicating immunity to scarlet fever. Furthermore, the first studies indicated that the Dick reaction in general was positive at the beginning of an attack of scarlet fever but during the course of the disease became negative indicating the production of antitoxin by the infected individual. It was also found that individuals giving a positive Dick reaction and presumably therefore susceptible to scarlet fever could be inoculated subcutaneously with increasing amounts of the toxin and after a certain length of time the skin reaction could be

rendered negative and in this manner the individual could be actively immunized against scarlet fever. Studies by Zingher indicated that the Dick reaction in young infants resembled the course of the Schick reaction very closely in that there appeared to be a hereditary transmission of antitoxin from mother to child and that antitoxin thus inherited was present in the child for a limited period of time. These studies seem to indicate a close analogy to similar phenomena observed in diphtheria.

However, as time went on and studies of the relationship of the toxic substance to scarlet fever were multiplied some doubt arose concerning the exactness of the analogy to diphtheria. In the first place, the so-called toxin was heat stable and required boiling for two hours to destroy it completely. It was also found that large amounts of the toxic substance could be injected into guinea pigs, rats and other animals without producing serious effects. Furthermore, it could be extracted from the bodies of the streptococci themselves. Other important discrepancies developed between the Schick and Dick reactions. It was shown that the Dick reaction in infants under six months of age are in general negative if relatively small amounts of toxin are used regardless of the presence or absence of antitoxin in the blood. As time goes on they tend to become positive and there is a progressive increase in sensitivity which reaches its maximum somewhere between the fourth and tenth years. In many instances the reaction becomes negative in scarlet fever sometime before the appearance of

demonstrable antitoxin in the blood. Furthermore, in certain individuals the reaction remains positive even after the acute attack of scarlet fever has subsided. Some interesting observations in relation to these phenomena have been made by Brockman. He has been able to cause the disappearance of a positive skin reaction within from twenty-four to forty-eight hours by subcutaneous injection of considerable amounts of toxin. Such an early disappearance of a positive reaction, of course, cannot be dependent upon the production of antitoxin but is more of the nature of a desensitization phenomenon such as is observed in instances of allergy. Brockman furthermore observed that individuals with a negative skin reaction could be made positive by injections of small amounts of toxin and a sensitiveness thus induced. All this work has been corroborated in animals. Laboratory animals give a negative skin reaction upon injection of a toxic substance. They can, however, be sensitized either with filtrate toxin or with the bodies of the organisms themselves. When this has been done the skin reaction becomes positive and such a positive skin reaction can readily be neutralized by scarlatinal antitoxin. There is no doubt that the skin reaction in animals is a hypersensitive phenomenon and that this hypersensitive reaction can be neutralized by an antiserum, the first example of such a phenomenon with which I am familiar. In animals also a positive skin reaction can be caused to disappear rapidly by a single intravenous injection of the filtrate substance. After the lapse of a certain



length of time the skin reaction in animals may again become positive and the whole series of events may be repeated. Somewhat similar observations have been made in human beings in that negative reactions have been observed to become positive and the negative again. These observations would seem to indicate that there are certain fundamental differences between the pathogenesis of scarlet fever and diphtheria. The so-called toxin of scarlet fever is in some ways similar to tuberculin and the positive skin reaction observed on the intracutaneous injection of scarlet fever streptococcus filtrate would seem to be dependent upon hypersensitiveness of the skin of this substance. It differs, however, from tuberculin in that upon injection into animals it gives rise to a neutralizing antibody. We now know that many bacteria give rise on growth in culture to similar filtrate substances. Some of these can readily be neutralized by antisera and others cannot. We now believe that the rash and acute toxic manifestations of scarlet fever are partly dependent upon the existence of a hypersensitive state in the infected individual. Very young children are insensitive to the products of the streptococcus of scarlet fever and therefore cannot have a typical attack which is characterized by the peculiar rash of scarlet fever. After a lapse of a certain length of time they seem to become sensitive to the products of streptococcus and if while in this sensitive state they become infected

with a suitable organism may have a typical attack of scarlet fever. As the individual becomes older repeated exposures to streptococci of one kind or another would seem to induce the production of a neutralizing antibody which from then on continues to circulate in the blood. When this state has been reached sufficient antibodies are usually present in the blood to prevent the appearance of typical scarlet fever, even if such an individual should become infected by one of the more highly toxic forms of streptococcus. These observations in scarlet fever have led to the formulation of certain interesting hypotheses in connection with infectious disease. They have centered interest upon the chemical constituents of bacterial cells and have led to the belief that an infected individual may respond in a highly specific way to each of the different chemical constituents of a micro-organism. The nature of the response to one such constituent may be so different from the response to another that the two series of events might even be looked upon as two quite different diseases. We might even think that one series of events would be quite definitely limited in time whereas the other may extend by a series of repetitions throughout the life time of the individual. Whether or not these studies will lead to a better understanding of the relationship of chronic degenerative types of disease to infection remains for the future to decide.

# The Relation of Chemical Influences, Including Diet and Endocrine Disturbances, to Epilepsy\*†

By H. RAWLIE GREYFERN, M.D., *New York City*

I HAD expected to speak in relation to epilepsy and endocrine disease, but the work along this line has not reached a stage where it is suitable to report it. I will, therefore, limit my remarks to three subjects. First, the effect of fasting and the ketogenic diet upon the course of epilepsy, second, the effect of the fasting and ketogenic diet upon the acid base equilibrium, and, third, I will tabulate the results of therapy as I have outlined it, with the old attempt to offer a tentative new classification of this condition.

Work was begun by us on the treatment of epilepsy in the early part of 1919. It was suggested by the results obtained by an osteopathic physician, Dr. Conklin, in Battle Creek, who happened to have fasted a young cousin of mine for relief of the condition. The result in his case was 100 per cent successful in arresting epilepsy over a four year period. Since then repeated fasts have been without avail,

and the disease is rapidly becoming more severe.

The first case we undertook for treatment was that of a child who had had epilepsy, both *petit* and *grand mal* attacks, at least ten to fourteen a day for fourteen months. The patient was a boy, aged 9, who was put on complete starvation after two weeks on general diet in a hospital. On the third day of the starvation he went into complete acidotic coma, from which he was pulled through on glucose injections. Since that date, about February 4, 1919, the patient has remained free from minor and major fits. Unfortunately for the others, the same results have not been obtained. We have now, at the end of nine years up to January 1, 1928, no case which we consider cured.

No cases are reported, whether a case on fasting or ketogenic diet alone, or with fasting, or considered an arrested case until at least a year has elapsed. I admit this is an arbitrary way of looking at it, but it helps to explain the great divergence in results that have been obtained by other men who have employed this treatment, Wilder, Talbot, Peterman and Helmholtz. The percentage of good

†Proof submitted to author but not returned, Editor

\*Informal address as part of a Symposium on Epilepsy, at the Twelfth Annual Clinical Session of The American College of Physicians, New Orleans, La., March 7, 1928

results in children is much higher the earlier the results are tabulated in the course of the disease after treatment

Since 1919 we have personally observed in the hospital and in the office 377 cases of epilepsy. These were only diagnosed as epilepsy after a competent neurologist gave a negative report as to the presence of any other condition, and X-ray examination of the skull showed nothing suggestive of anything other than idiopathic epilepsy. In all but six of these cases the original diagnosis seems to have been established by the subsequent course. The total number treated was 117, those by the ketogenic diet and by fasting, or by fasting alone numbered seventy-nine. The patients were about evenly divided between the two sexes. Of these seventy-nine, fifteen only remain arrested cases today. Six of those fifteen, nearly one-half of the total number of arrested cases, received no treatment other than one period of starvation lasting from three to fifteen days. We have not considered any patient a child who is over fifteen.

Among the remaining cases in this series of 377 there were several adults. Only one adult has had his epilepsy permanently arrested for a period of over two years, and that was interrupted by the fasting. She has now been free from any attacks for seven years. She received a five day fast and then went free for six months had one major seizure and since then has had no attacks.

In addition to the fifteen cases reported as arrested in the 115 children aside from the seventy-nine in the thirty-eight remaining various

forms of treatment, luminal, bromides, anti-constipation procedures, potassium borotartrate, enucleation of the tonsils, and so on, have been carried out. I have recorded one case as treated by meningitis, meaning that subsequent to an attack of cerebrospinal fever the child had no attack for four years. Three of the patients had complete arrest for two years from correction of constipation alone. One case was interesting in this respect, in that the attacks stopped as soon as two regular bowel movements a day were secured instead of a single one. Two patients have remained apparently cured as the direct result of enucleation of tonsils. Six of the fifteen arrested cases have had no ketogenic diet.

Our low percentage of arrested cases, which range from two to nine years, is not in accord with the results reported by Helmholz, Peterman and Talbot, but I think the time elapsed with all these investigators has not been sufficiently long to judge as to whether or not the percentage of arrests will remain as high as at present. For instance, in the report of Dr. Talbot there are twelve cases in children who were selected for this treatment in that they showed no evidence of mental deterioration. Our cases were not selected from that point of view and nine out of the twelve remained completely arrested from three to nine months which about covers the period of their observation. On the contrary, Helmholz reports 291 children on a ketogenic diet under observation for five years and reports but 40 and 42 per cent good results. Our own series gives

an arrest in about 20 per cent I think when the other series have run for longer periods the percentage will be about the same

This does not sound like a very impressive therapeutic achievement, but when one considers the results obtained by other means than fasting and ketogenic diet, which may be spoken of as our control group, there has been no other case arrested. We have not consciously picked for fasting and the ketogenic diet those children without mental deterioration or other stigma, including family history. We have tried to have the same number of cases of what were looked upon as hopeless receive the ketogenic and the other treatment. The contrast then between the groups is rather striking, but an arrested epilepsy even over periods as long as ten or fifteen years does not give any key to the cure of the disease, and I am dubious as to what the future will bring forth in regard to the disease.

Another thing is the administration of the ketogenic diet. It is a very hard diet to keep up over long periods with the majority of children and the order of intelligence of their parents, as other observers have noted, so failure to achieve results with this diet is undoubtedly, as Helmholtz pointed out, due to inability to stick to the diet.

In searching for some explanation as to why the fasting seemed to have some effect and the ketogenic diet had also, two theories have been proposed by the men who have employed this treatment. Some have felt that it was due to acidosis, and that if they could produce an acidosis they could control the number and severity

of the seizures, while producing an alkalosis would tend to produce seizures. Dr. Kalb and myself have been able to bring about seizures during starvation when this had apparently stopped the seizures. We have been able to bring on a complete reversion to the epileptic state by giving large doses of sodium bicarbonate. However, it is quite plain that the treatment is not responsible for the condition observed. This is brought out by the fact that producing a ketonuria does not affect the course of the epilepsy. In one instance it apparently did for ten weeks, but in others no results were achieved. Dr. Wilder believes that the diacetic acid is capable of producing an ether-like radical and that this acts as an anesthetic on the nervous system. He finds the results when there is an acidosis produced by ketoacids but not when produced by other acids.

In the slide shown the blood hydrogen-ion concentration on two normal individuals is given. You will notice that we have arbitrarily picked  $7.34^{\circ}$  and at least 90 per cent of our observations of normal individuals fall within this area. You will see that there is a distinct acidosis at this period (indicated), and after the starvation was over the chart swung as you see it here. There was a greater tendency in the epileptics to have a more varied swing in the hydrogen-ion concentration of the blood.

(Slide) This chart represents the fasting period, and this (indicating) the resumption of attacks on normal diet. You will notice the big swing in the hydrogen-ion concentration, reaching a high degree of acid here

(indicating) and then followed by a big shoot with an outbreak of nine convulsions over a period of four days. Unfortunately, we did not have the hydrogen-ion determinations during the fasting, but we have it here, when it went down 32 volumes in percentage.

(Showing slide) This shows the determination of seventeen normal individuals. The vast majority of these fell within the normal age range, a few on the extreme acid side and a few toward the alkaline side of normal.

In closing, I would like to offer as a suggestion, that we attempt to form a standard, if only from the standpoint of therapeutics, to suggest a new classification of the disease commonly spoken of as epilepsy. If one can judge from the general downward trend in any form of treatment, particularly the failure of certain groups of children to respond to starvation and the ketogenic diet, one is impressed with the fact that this group falls almost exclusively in the mentally deteriorated, in those who owe this to long continued use of bromide and luminal, and those who come under one year of age. These results coincide with those in the other clinics.

It is interesting that in all this series over 92 per cent achieved their epileptic manifestations before the twentieth year. That is in correspondence with Dr. Geyer's statistics obtained in analyzing several hundred cases.

I bring this out only because it shows that we are fairly safe in classifying them during the childhood age, for that group that occupies a percentage of our state hospitals. Perhaps that has something to do with explaining the poor results Dr. Allen had when he fasted sixty epileptics in the New Jersey State Home for Epileptics. The majority of these patients are mentally deteriorated. If we adopt some other term for that group, spasmophilia or what you will, it may be possible to divide that group into three, four or five sub-groups. One would fall into those due to the allergic reaction, another perhaps to instability of the circulatory system, a third small group to endocrine disturbance, and so on. There are other possibilities which time will not allow me to take up, but only by attempting to class our cases in this way will we be able to achieve half way satisfactory therapeutic results, and I think in this way we can simplify investigation as to the etiology of the disease.

Last of all, if the medical profession as a whole, can remove the term epilepsy from the majority of cases or what are today called epilepsy, it will bring great comfort to many individuals. The results of fasting and the ketogenic diet are apparently the best that are obtained by any therapeutic procedure that we have to offer to epileptics in childhood today.

# Ureteral Stricture as a Cause of Attempted Suicide\*

By MITCHILL BERNSTEIN, M D , *Philadelphia, Pa*

**I**N view of Hunner's teaching of the possibility of ureteral stricture simulating a variety of acute and chronic abdominal conditions, the following case report of attempted suicide due to the pain of an ureteral stricture, I believe, is of more than academic interest

## *Case Report —*

C R, aged 44, female, married, was admitted to the Jewish Hospital on May 2, 1928, in an unconscious condition as a consequence of illuminating gas poisoning, the gas being taken with suicidal intent. After resuscitation, the patient stated that she attempted suicide since she has suffered unbearable abdominal pain, from which she was unable to obtain any relief, and preferred death to the continued agonizing pain. Her father died of diabetes at 67, and her mother died of carcinoma of the liver at 58. One brother, aged 48, was living and well. There was no history of any mental disease in the family.

## *Personal History —*

The patient had pneumonia, measles, and whooping-cough during childhood. Menstruation began at 13. She married at 25, and had three children, of which two were twins. One of the twins died at five and one-half months, and the other at 12 years of age.

The patient's present illness dates from 1923, when she first developed severe pain in the upper right abdomen. The pain was

intermittent in character. It radiated to the back and right shoulder. Nausea and belching always accompanied the attacks of pain, but vomiting occurred only occasionally. A sense of abdominal constriction, beginning at the right upper abdomen, often occurred with the onset of pain. These attacks of pain varied from several minutes to several hours in duration. She was never jaundiced.

In an effort to obtain relief from symptoms, a hysterectomy, together with an appendectomy and pelvic repair was performed sometime in 1923. Operative procedure did not relieve the symptoms. The constant pain following the operation prompted her to consult a number of physicians as well as a number of clinics at various hospitals. She was told she had gall bladder disease, for which she was treated. The various treatments were of no avail, each succeeding attack becoming so excruciatingly painful, the patient became desperate, and attempted suicide on May 2, 1928.

## *Physical Examination —*

The patient was a fairly well-nourished white female. She had a slightly yellowish pigmentation on forehead and side of the face. The skin was dry and somewhat thickened. The eyes, nose and throat were normal. The neck was normal. Examination of the lungs and the heart proved negative. The abdomen was relaxed and a scar of the previous operation was present. The liver and spleen were not enlarged. There was no tenderness over the gall bladder region. Bi-manual palpation of the right kidney caused a great deal of pain, although the lower pole of the right kidney was barely palpable. The left kidney was not palpable. The reflexes

\*From the Medical Service of Dr Bernard Kohn, Jewish Hospital, Philadelphia, Pa.



X-Ray Plate Showing Ureteral Stricture

were diminished. The blood pressure was 120 systolic, and 80 diastolic.

Laboratory investigations, including examination of the urine, blood, blood chemistry, Wassermann reaction, gastric analysis, biliary drainage, and X-ray of the gall bladder all proved negative.

*Comment —*

The history and physical examination suggested the possibility of right ureteral stricture. The ureteroscopic examination, and pyelographic studies confirmed the clinical diagnosis.

The stricture was found at the extreme upper end of the right ureter. (Plate No. 1 shows clearly the site of the ureteral stricture.)

The X-ray report states as follows:

"The opaque catheter extends as far as the inferior aspect of the fourth lumbar

vertebra on the right side. There was some dilatation of the ureter in the lower lumbar sacral region, and narrowing immediately before it reached the pelvis of the kidney. The pelvis of the kidney seemed larger than normal. The calices are well-defined, and show nothing abnormal. There was no shadow of calculus seen in the urinary tract."

On May 22, 1928, bougies numbers 4, 5, and 6 were passed the entire length of the right ureter, although resistance was felt to the number six. The patient was relieved following the ureteral dilatation, and was discharged from the hospital May 23, 1928, with instructions to report at stated intervals for continued treatment.

The ureteroscopic examinations were made by Dr. John B. Lowmes.

The X-ray studies were made by Dr. Sidney L. Feldstein.



# Our Changing Profession\*

By THOMAS B. COOLEY, *Detroit, Michigan*

THESE somewhat random thoughts are the result of cogitation over a questionnaire from the Council on Medical Education, which I daresay some of you also received, and to answer which satisfactorily would involve consideration of the history and development of medicine, the past and present status of the medical profession, in itself and in relation to the community, and possible changes due on the one hand to the advance of science, and on the other to developments in the general social structure.

It is the veriest commonplace to say that there has been, within the past quarter century, a very great change in the relations of the members of the so-called learned professions to the other classes of the community, and in the nature of the regard in which they are held. My father, and most of yours, were dignified old gentlemen in plug hats at forty-five, holding themselves, if not exactly aloof, at least a little apart from the merchant, the manufacturer, and the banker, and looked up to by all classes for a real or supposed intellectual and cultural superiority, and in the case of the physician, because of a certain glamor of mystery at-

tendant on a calling quite beyond the layman's ken. This honorable position in the community went far, in the case of the minister and the physician, to make up for the disparity in the financial returns between these callings and the more lowly business pursuits.

Certain modern developments have wrought great changes in all social relations, especially in the United States. The progress of mechanical invention, railway, telegraph, telephone and radio, the automobile and the accompanying road building, have made communication universal, and supplied numberless common interests to classes whose callings formerly kept them far apart. The universal vogue of sport has played its part. When every other man in the country is at once a golfer, a baseball and radio fan, and perforce, an automobile mechanic, the bars between classes can no longer be very high.

The mystery of learning, too, is no longer what it was. The average man is at least superficially, if not really, better educated than formerly, and through his newspaper and innumerable magazines and novels, feels himself quite conversant with the progress of the world. If he lacks real learning and culture, he doesn't know it.

\*Presidential address, Detroit Academy of Medicine, 1927

spect and love our profession is to see that its dignity and prestige are maintained in the face of the rising tide of commercialism. If I were obliged to make suggestions as to what is particularly needed in medical education, I think I should say that, under present day conditions it would better begin by a careful selection of candidates from the standpoint of character as well as from that of early education and mental capacity. In saying this, I am not implying that the character of the average medical student is low, but thinking of the probability that the tendency toward a lowering of professional standards is likely to increase.

Assuming a selection of students on this basis, I should like further to

see more emphasis laid on high ethical standards and professional ideals throughout the training period. Here, of course, the example of the right kind of teachers is of the greatest value, but I think that there might be something more than this, in the way of conscious deliberate effort to implant and foster such ideals, than is now made in most schools. I think, too, that more might be done to the good of the profession to stimulate in the student a desire for as high a degree of general culture as possible. This, as I have said, can hardly be a matter of the required curriculum, but I can think of more than one other means, especially in the campuses of the great universities, if it be made a matter of serious effort

## Editorial

### *GENERALIZED XANTHOMATOSIS*

Rowland (Archives of Internal Medicine, November, 1928) makes an important contribution to our knowledge of xanthomatosis in the correlation of a group of cases described as defects in membranous bones, exophthalmos and diabetes insipidus (Christian's syndrome). He considers fourteen cases all occurring in early childhood, six of the patients being girls and eight boys. In ten of the cases the probable onset of the affection occurred during the second year of life, with one each in the third, fourth, sixth and seventh year. In all cases the onset was insidious and periodic, so that in most cases the disease was well advanced before a physician is called. The family history was negative in all cases save one in which the mother had hypercholesterinemia. Obstetric histories were normal. During the first year, nutritional disturbances did not occur, and development was normal. The blood Wassermann was negative, and tuberculosis was not present. One of the common infections of the age antedated the onset in most instances. In three cases a history of trauma was associated with some of the bone defects. The symptoms depended on the location of the lesions, the extent of involvement and the mechanical effects resulting from

was a notable lack of subjective symptoms, but during the active stage there was frequently increased irritability, and often tenderness and pain referred to the lesions. The most notable clinical feature was the occurrence of diabetes insipidus in all of the series except two. Glycosuria was found in one case only. Retardation in growth was apparent in most instances from the onset of symptoms. In two cases besides dwarfism, a typical dystrophia adiposogenitalis developed. The varying degrees of exophthalmos which occurred in every case may be explained by the destructive bone process. The fundi in every patient examined were normal. Lesions of the skin suggesting xanthoma were not found in any one of the cases. Lipemia was not observed in any instance, there was usually a slight degree of anemia with a moderate increase of leukocytes. In one case the blood changes were so marked as to lead at first to a diagnosis of anemia pseudoleukemia infantum. Evidences of blood destruction were not found in the case, but the severe anemia was due to the hyperplastic process in the long bones interfering with blood formation. Four of the group came to autopsy. In all the fatal cases there was an extreme degree of pulmonary fibrosis with lipoidosis of the new-formed tissue. There have been seven deaths in all and as far as known



structure adjacent to the defect appeared normal. The frequent presence of foreign-body giant cells in the lesions, in association with pressure, suggests the explanation for the bone destruction. An early symptom observed in the majority of the cases was an irritated condition of the gums, with loosening of the teeth. The teeth themselves appeared normal, except for erosion of some of the cusps. This condition resulted from xanthoma nodules arising from the periosteum covering the maxillary bones. There were many foreign-body giant cells in these tumor-like xanthoma masses with the same bone destruction present. As to the occurrence of diabetes insipidus it is possible that xanthomatous lesions found at the base of the skull, surrounding the hypophysis and occasionally involving the posterior lobe of the pituitary body, may through pressure or irritation be the cause of the diabetes insipidus, or there may be primary lesions in the hypophysis. Christian and Schüller regarded the syndrome as probably due to a primary disturbance of pituitary function, and various other observers explain disturbances of lipid metabolism as the result of disturbed function of certain endocrine glands. Rowland believes that the metabolic disturbance is primary, and that the evidences of disturbed hormone action on the part of the endocrine is the result of the pressure of the xanthomatous reticulo-endothelial hyperplasia in these glands. The special service rendered by Rowland in this extensive study of his on the syndrome "defects in membranous bones, exophthalmos, and diabetes insipidus," lies in his

correlation of the many forms of localized or generalized visceral xanthomatoses of the reticulo-endothelial system, under the conception of a lipid metabolic disease of the reticulo-endothelial system—a *lipoid gout*. On the one hand are the yellow to yellowish-brown lipid-containing xanthomas, endotheliomas, angiomas, giant cell tumors, and giant cell fibrosarcomas of the periosteum, fascia, tendon-sheaths, peritoneum and pleura, skin, etc., that are not autonomous new growths but represent lipid-storage tumors. On the other hand, Niemann's disease is the rapidly developing xanthoma of infancy, while Gaucher's disease represents a similar condition with an infiltration of more complex lipoproteins, and the various generalized xanthomatous deposits associated with diabetes mellitus or glycosuria, icterus and certain affections of liver or kidneys—all represent primary disturbances of lipid metabolism. Each of these conditions differs in clinical form, in the pathologic structure of the lesions and in the nature of the lipoids concerned, but they all represent the same irritative proliferation of connective tissue elements—reticulo-endothelial hyperplasia, in other words, there is no essential difference between Niemann's disease, Gaucher's disease, Christian's syndrome, and the many forms of xanthoma. They are all manifestations of the same pathologic process, modified by certain differences in the patient's general metabolic state. The recognition of the fact that underneath all of this varied symptomatology there is a *hyperlipidemia* is of the greatest importance in suggesting the methods of treatment to be followed.

# Abstracts

*Klinische and Experimentelle Beiträge zur Frage der Hodentransplantation* By DR L. SCHONBAUER and DR F. HOGENAUER (Archiv f. Klinische Chirurgie, May 15, 1928)

In the literature of the last several years the question of the transplantation of the testis has received much attention, and the effects of auto-, homo-, and heterotransplantation have been extensively studied. The experimental investigations of Voronoff and their clinical applications have appeared to open up a new field of work. The question of the rejuvenescence of the senescent organism stands in the foreground of the Voronoff investigations. This observer has developed his own method of operation, which consists essentially in the transplantation of the testis upon the tunica vaginalis. According to Voronoff the testis of a chimpanzee transplanted in this way into a man showed, on histological examination, fifteen months later, preserved epithelial cells in the seminal tubules. Through such testis transplantations Voronoff claims to produce a rejuvenescence both in the case of man and in animals. In his book, "Prevention of Age through Artificial Rejuvenescence," he has described a number of successful operations in man and animals. Other authors have confirmed the rejuvenating effects of testicular transplantation. Max Thorek confirms the value of homo- and heterotransplantation of the testis in 97 cases of his own, and claims to have obtained healing in 31 cases and an essential improvement in 28 cases of senility, defect of testes, neurasthenia, impotency on non-organic basis, and dementia præcox. Homotransplantation succeeded much better than heterotransplantation. Among others reporting similar good results are Hunt, Falcone, Wilker in the case of inguinal testis, Stanley with injection of testicular extract and testis transplantation (testes of cadavers into living men), Lichtenstein in a clinical

observation extending over years, Lydston, Mühsam, Pfeiffer, McKenna and others. Opposed to the results and opinions offered by the above workers stands a long series of observations by numerous workers who deny that testis transplantation has any effect upon the organism. Enderlen opposes Voronoff's views on the ground of four cases, in which microscopic examination made several weeks after the transplantation showed only necrosis and fatty degeneration of the transplanted organs. To the same results and the same opposing views come Kreuter, Lexer, Förster, Hamesfahr, Buchhardt and Hilgenberg, Brandt and Lieschied (who attained a transitory result) and Kurtzahn who regarded the effects of the transplantation as due to resorption processes and not due to the action of living cells. Haberlandt has shown in a large series of experiments that every autoplasmic transplanted testis undergoes necrosis, no matter by what technical method, or where it is transplanted. The contradictory results offered in the literature led the present workers to study the results of auto- and homotransplantation in Rhesus apes. From their results in 13 cases in which the transplants were examined histologically in serial sections it is shown conclusively that free transplanted testis tissue undergoes necrosis and is absorbed, no matter whether implanted intra- or extraperitoneally or according to the method of Voronoff in the tunica vaginalis. As early as 2½ months after the transplantation the transplanted testes are wholly fibrous and atrophic, and are still recognizable, even after 3 and 5½ months. In the intraperitoneal and extraperitoneal implants in some cases nothing of the testis remains or only scar tissue was found. In one case there was found a completely atrophic testis. It appears striking that in a large number of the experiments no testicular remains could be found at the place of implantation, only scar tissue remained, where a transplant was present.

## Reviews

*The Peaks of Medical History An Outline of the Evolution of Medicine for the Use of Medical Students and Practitioners* By CHARLES L. DANA, A.M., M.D., LL.D., Professor of Nervous Diseases, Cornell University Medical College, Late President of the New York Academy of Medicine, etc. 105 pages, 40 full-page plates and 16 text illustrations. Second Edition. Paul B. Hoeber, Inc., New York, 1928. Price in cloth, \$3.00.

The first edition of this work appeared in April, 1926, and the fact that a second edition is called for within so short a time must be encouraging both to the author and his editor. No especial change has been made in this second edition. A few illustrations have been added, and some practical criticisms involving minor slips in the wording of a legend, or some inaccuracy in typography have been carefully attended to. Comments on the work, so far made, have been mostly those of approval. The object of this short history of medicine has been, as we pointed out in our review of the first edition, the presentation chronologically of the main facts of the evolution of medicine from pre-Hippocratic times, down to the middle of the nineteenth century, giving a rapid survey of the special movements marking the progress of medical science. The high spots, or peaks in the evolution of medicine are so emphasized that the student can in a short time obtain a visualization of the subject as a whole, and in this way acquire a background upon which he can work out details in accordance with his interests and tastes. Six peaks, that of Hippocrates, the Alexandrian School, Galen, the Renaissance, Harvey and Jenner mark the seven periods into which the history of medicine naturally falls. These peaks are shown in a diagram on the first page. After a brief opening chapter on ancient medicine there follow six

main chapters of exposition according to this diagram, and these in turn are followed by a chapter of bibliographical notes on books to be read by the student in his further studies in medical history. The illustrations form an especial feature of the book, in that they are *kinetic* rather than static in character, and intended to give social atmosphere to a text which is preponderately biographical. We can only repeat here what we said of the first edition. The material used in the text is excellently chosen, and presented in an agreeable readable manner. The book fulfills its aims in a high degree of excellence. It is beautifully printed, the illustrations are excellent, and the full page printings of the Oath of the Hindu Physician and the Oath of Hippocrates add to the general impression of fine workmanship which the book gives as a whole. We recommend this work highly, both to students and to practitioners, in that it offers a systematic presentation of the high spots in medical history.

*The Clinical Examination of the Nervous System* By G. H. MONRAD-KROHN, M.D., F.R.C.P., Professor of Medicine in the Royal Frederick University, Oslo, Physician-in-Chief to the Neurological Section of the State Hospital, Oslo, Also in Charge of the Hospital's Out-Patient Department for Nervous and Mental Diseases, Corresponding Member of the Neurological Societies of Paris, Copenhagen, and Estonia. With a Foreword by T. GRAINGER STEWART, M.D., F.R.C.P., Physician to the National Hospital for the Paralyzed and Epileptic, Queen Square. Neurologist to the West London Hospital. Physician to the Central London Ophthalmic Hospital, Consulting Neurologist, The Queen's Hospital, Sidcup, and Queen Mary's Hospital, Roehampton. Corresponding Member of the Neurological

Society of Paris. Fourth Edition 200 pages, 55 illustrations Paul B Hoeber, Inc, New York, 1928 Price in cloth, \$2.50

This book is not a translation, but has been written in English by Dr Monrad-Krohn himself. Hence the book is free from that vagueness of meaning which is common to so many translations. At times the author's mode of expression may strike the reader as unfamiliar, he always succeeds in making his meaning clear and in emphasizing his point. The third English edition was printed in 1926, and its continued success has necessitated the publishing of this fourth edition. In this book the author describes a routine method of examination of the nervous system which he has adopted in his neurological clinic, and has given an outline of the clinical tests which he himself considers to be the most practical and useful. He has shown an appreciation of the true needs of the neurologist and psychiatrist in that he had not confined his book to the purely neurological aspects of nervous disease, but includes an outline of the examination of the mental state of the patient. He insists upon the importance of combining a knowledge of neurology with that of psychiatry. He further emphasizes the fact that proficiency in neurological examination can only be obtained through practice, and that his book is intended for use in close connection with clinical work. For the present edition he has again revised the book, making some minor additions and alterations. In the choice and description of the various methods the author has been guided by experience gained in the daily work in his clinic. A short chapter on the interpretation of x-ray pictures of the skull has been added, which gives a few points which according to his experience, both the beginner and the practitioner are apt to overlook or to misinterpret. The contents include the Anamnesis, the Status Præsens, including the mental state, the cranial nerves, motor system, associated movements, coördination and cerebellar signs, the sensory system, including superficial sensation, deep sensation, combined sensation, sensory paths and

segmentation, the reflexes, including the deep reflexes, cutaneous reflexes, reflexes of spinal automatism, postural reflexes, organic reflexes, and reflex formulae, the standing position, the gait, simulation, electrical examination; the examination of cerebro-spinal fluid, and puncture of cisterna magna. The main method of routine neurological examination is then followed by appendices on the Binet-Simon tests, psychosomatic examination, diplopia, vestibular tests, anatomical diagrams, pharmacological tests of the vegetative nervous system, the interpretation of x-ray photographs of the skull, on repeated examinations and on the first routine examination. All in all, this book represents the most complete and best abridged method for the clinical examination of the nervous system that has yet been published. It has been brought thoroughly into line with the results of recent medical research. Of especial practical importance is the author's emphasis of the fact that the neurological examination without an adequate investigation of the patient's mental condition is incomplete, and that the psychiatric examination is equally incomplete unless accompanied by a complete neurological examination. The author gives wise advice to medical students in the following procedure of examination. "First, complete the systematic examination, give the examination your whole attention without speculating about the diagnosis until the examination has been completed. Then write out a tabulated list of your findings, it is most convenient to arrange them in two columns corresponding to the two sides, Right and Left. Next, try to arrive at a *focal diagnosis* based on your anatomical and physiological knowledge. Finally, consider the *nature* of the lesion, aided by your knowledge of general pathology." We recommend this little book most warmly as a guide to neurological examination.

*Roentgenology Its Early History, Some Basic Physical Principles and the Protective Measures* By G W KAYE, O.B.E., M.A., D.Sc., F.Int.P. 157 pages, 49 illustrations Paul B Hoeber, Inc, New York, 1928 Price in cloth, \$2.00



This monograph represents an expansion of the author's Caldwell lecture, given in 1927, before the American Roentgen Ray Society's meeting in Montreal. It is a reprint with additions, from the American Journal of Roentgenology and Radium Therapy, Volume XVIII, No. 5, November, 1927. In the present volume, the earlier chapters particularly, which touch on certain historical and physical aspects of roentgen-rays have been enlarged and expanded by various additional material. The later chapters have been written particularly for hospital authorities who seek to improve the working conditions in their roentgen-ray departments. The opportunity has been taken to include the International Recommendations which were adopted at the Second International Congress of Radiology held in Stockholm, in July, 1928. The ten chapters of the book are given up to I, Some Early Philosophers, II, The Nature of Roentgen Rays, III, Total Reflection of Roentgen Rays, IV, Prismatic Refraction of Roentgen Rays, V, Diffraction of Roentgen Rays by Ruled Gratings, VI, The Nature of Radiation, VII, Roentgen-Ray Protection, VIII, Measurement of Protective Values, IX, Working Conditions in Roentgenographic Departments, X, The Future of Roentgenology. These are followed by the References and Appendices A and B. Of particular interest are the illustrations, many of which are reproductions of interesting old prints, showing early scientific experi-

ments in the attempt to produce a vacuum, and the production of electric discharges *in vacuo*. Hauksbee, about 1705, was the first to conduct experiments along the latter line. In 1740, the Abbe Nollet, devised the "electric egg," which was not an unsuitable term for the prototype of the roentgen-ray bulb. It was Morgan, who in 1785, was able to obtain so good a vacuum that an electric discharge was prevented from passing, and who probably was the first to generate x-rays, had he but known it. By the end of the 18th century the electric discharge tube was an established fact. Progress was more rapid during the 19th century, when Davy, Faraday, Geissler, Plücker, Hittorf, Crookes, Lenard and other noted workers brought the line of development up to 1895 and the discovery by Roentgen of x-rays, when the science of radiology or roentgenology was brought into being. The subsequent history of the development of radiology is told in a discussion of the chief features in the next several chapters. The remaining portion of the book is given up to a consideration of roentgen-ray protection, protective values and the working-room conditions of x-ray departments. Aside from the interest of the historical sketch of the scientific experiments leading up to and preceding the discovery of x-rays, the book has a practical value in the soundness of the principles of protection advocated. It may be recommended to any student interested in roentgenology.

# College News Notes

## PROGRAM THIRTEENTH ANNUAL CLINICAL SESSION

### BOSTON COMMITTEES

JAMES H. MEANS, *General Chairman*

### COMMITTEE ON ARRANGEMENTS

JAMES H. MEANS  
WILLIAM B. BREED  
HENRY A. CHRISTIAN  
RANDALL CLIFFORD  
CHESTER M. JONES  
ELLIOTT P. JOSLIN

ROGER I. LEF  
GEORGE R. MINOT  
JOHN H. MUSSER  
JOHN PHILLIPS  
JOSEPH H. PRATT  
FRITZ B. TALBOT

CONRAD WESSELHOEFT  
FRANKLIN W. WHITE

### COMMITTEE ON HALL

FRANKLIN W. WHITE

### COMMITTEE ON CLINICS

HENRY A. CHRISTIAN  
CHESTER M. JONES  
ELLIOTT P. JOSLIN

GEORGE R. MINOT  
JOSEPH H. PRATT  
CONRAD WESSELHOEFT

### COMMITTEE ON ENTERTAINMENT

RANDALL CLIFFORD

WILLIAM B. BREED

FRITZ B. TALBOT

### PRELIMINARY PROGRAM ANNUAL CLINICAL SESSION THE AMERICAN COLLEGE OF PHYSICIANS APRIL 8-12, 1929

Monday, April 8, 1929

OPENING SESSION, 2 30 O'CLOCK

Hotel Statler Ballroom

1 Addresses of Welcome David L. Edsall, Dean of Harvard Medical School  
Alexander S. Begg, Dean of Boston University Medical School  
A. Warren Stearns, Dean of Tufts College Medical School

John M. Birnie, President of Massachusetts Medical Society  
Lincoln Davis, President of Suffolk District Medical Society

2 Reply to Addresses of Welcome  
Charles F. Martin, President of The American College of Physicians

3 Tuberculosis A Confession of Faith  
Lawrason Brown, Saranac Lake, N. Y.

4 (Title not yet announced) Lewellys F Barker, Baltimore

5 Juvenile Diabetes I M Rabinowitch, Montreal

6 Glycosuria James E Paullin, Atlanta

7 Clinical Aspects of Paroxysmal Hypertension M C Pincoffs, Baltimore

EVENING SESSION, 8 00 O'CLOCK  
Hotel Statler Ballroom

*Symposium on Deficiency Diseases*

1 The Fundamental Nature of Deficiencies George R. Minot, Boston

2 Pathology of Deficiencies S Burt Wolbach, Boston

3 Biochemistry and Physiology of Deficiencies George R Cowgill, New Haven

4 Pellagra Joseph Goldberger, Washington, D C

5 Pernicious Anemia Randolph West, New York.

Tuesday, April 9, 1929  
MORNING, 9 00 TO 12 00 O'CLOCK  
Hospital Clinics

AFTERNOON, 2 30 TO 5 00 O'CLOCK  
Hotel Statler Ballroom

1 Fatigue and Infection W L Holman, Toronto

2 Neoplasms J B Murphy, New York

3 Specific Dynamic Action of Protein, Fat and Carbohydrate in Altered States of Nutrition Edward H Mason, Montreal

4 The Relation of Neisserian Infection to the Various Types of Arthritis O H Perry Pepper, Philadelphia

5 The Fallacy of Vaccine Therapy Charles C Bass, New Orleans

6 The Treatment of Angina Pectoris Harlow Brooks, New York

7 The Coronary Problem Arthur R Elliott, Chicago

8 Clinical Aspects of Trichiniasis Lewis A Conner, New York

9 An Intensive Clinical Study of a Graphic Method of Recording Blood Pressure Louis F Bishop and Louis F Bishop, Jr, New York.

EVENING SESSION, 8 00 O'CLOCK  
Hotel Statler Ballroom

1 Psychiatry in Relation to Medicine Austin F Riggs, Stockbridge, Mass

2 Syphilis of the Adrenals and Its Relationship to the So-called Idiopathic Addison's Disease. Aldred S Warthin, Ann Arbor

3 Lung Syphilis R I Rizer, Minneapolis

A smoker will follow this session

Wednesday, April 10, 1929  
MORNING, 9 00 TO 12 00 O'CLOCK  
Hospital Clinics

AFTERNOON, 2 30 O'CLOCK  
Hotel Statler Ballroom

1 The Treatment of General Paresis Harry C Solomon, Boston

2 Psychiatry's Part in Preventive Medicine Arthur H Ruggles, Providence.

3 The Need of Emotional Data in the Medical History John Favill, Chicago

4 Milder Forms of Coronary Obstruction James B Herrick, Chicago

5 The Failing Heart of Middle Life David Riesman, Philadelphia

6 Hypertension George C Hale, London, Ont.

7 Undulant Fever in the United States George Blumer, New Haven

8 (Title not yet announced) Robert A Cooke, New York

9. Tobacco Smoking and Gastric Symptoms Irving Gray, Brooklyn

EVENING SESSION, 8 00 O'CLOCK  
Hotel Statler Ballroom

1 Serums and Vaccines in the Prevention and Treatment of Disease Benjamin White, Boston

2 Clinico-Röntgenological Conference M C Sosman and Associates, Boston

Thursday, April 11, 1929  
MORNING, 9 00 TO 12 00 O'CLOCK  
Hospital Clinics

AFTERNOON, 2 30 O'CLOCK  
Hotel Statler Ballroom

1 The Treatment of Acute Asphyxia Cecil K Drinker, Boston

2 The Significance of Abnormal Metabolic Features in the Management of Thyrotoxicosis Walter W Palmer, New York

3 Can or Will the Internist Practice Preventive Medicine? George H Bigelow, Boston.

4 Factors in the Prognosis of High Blood Pressure W W Herrick, New York

5 The Carotid Sinus Reflex (Hering), Its Use in the Diagnosis and Treatment of Certain Cardiovascular Diseases C Saul Danzer, Brooklyn

6 Lead Poisoning from Snuff Raymond J Reitzel, Galveston

The General Business Meeting of The College will be held at 4 00 in the Hotel Statler Ballroom All Masters and Fellows should attend

EVENING, 7 00 O'CLOCK

Annual Banquet of The College

To be followed by a Dance

Address George E Vincent, President of Rockefeller Foundation

Friday, April 12, 1929

MORNING, 9 00 TO 12 00 O'CLOCK

Hospital Clinics

AFTERNOON, 2 30 O'CLOCK

Hotel Statler Ballroom

1 Motion Picture Demonstrating Its Value in Teaching Electrocardiographic Interpretations of Cardiac Arrhythmias Joseph B Wolffe, Philadelphia

2 Dr William Dunlop and Pioneer Canadian Medicine J W Crane, London, Ont

3 Rheumatic Fever Homer F Swift, New York.

4 (Title not yet announced.) J. C. Meakins, Montreal

5 Results to Be Expected in Malignant Disease Treated by Radiotherapy George E Pfahler, Philadelphia

6 The Problem of the Nervous Patient. Charles H Nielson, St. Louis

7 Endogenous Obesity—A Misconception L H Newburgh and M W Johnston, Ann Arbor

EVENING SESSION, 8 00 O'CLOCK

Hotel Statler Ballroom

Convocation Exercises

The General Profession is cordially invited No special admission tickets are required.

1 Convocation Ceremony

2 President's Address Charles F Martin, Montreal

### PRELIMINARY PROGRAM OF SPECIAL CLINICS AND DEMONSTRATIONS

This year the general session will be held in the afternoons and evenings, while clinics and demonstrations will be held in the mornings from 9 00 to 12 00

Special Admission Cards required. Clinic reservation forms and full directions will accompany the Final Program Reservations may be made by mail or daily at the Registration Bureau

Special clinics and demonstrations will be held as follows

A

BETH ISRAEL HOSPITAL

Program in charge of Herrman L Blumgart

B

## BOSTON CITY HOSPITAL

1 (A guest will give a clinic at this time, the name will be announced later)

2 The Progress of the Boston City Hospital John J Dowling, Superintendent

3 Treatment of Pneumonia Demonstration of Cases Edwin A Locke

4 Clinic of Unusual Cases Francis W Palfrey

5 Pernicious Anemia Demonstration of Cases William B Castle

6 Treatment of Anemias Demonstration of Cases George R. Minot

WEDNESDAY, APRIL 10, 1929

1 (A guest will give a clinic at this time, the name will be announced later)

2 Gastro-Intestinal Cases Franklin W White

3 Cardiac Cases William H Robey

4 Nephritis Cases William R Ohler

5 The Surgical Treatment of Pulmonary Tuberculosis Demonstration of Cases Edward D Churchill

Hypertension and Arteriosclerosis Demonstration of Cases Soma Weiss

THURSDAY, APRIL 11, 1929

1 Cardiac Cases Edward N Libby and Thomas J O'Brien

2 A Case Illustrating the Value of the Electrocardiogram James M Faulkner

3 Epilepsy William G Lennox.

4 Diseases of the Coronary Vessels Demonstration of Cases Joseph T Wearn

5 Peptic Ulcer Demonstration of Cases Maurice Fremont-Smith

6 Neurological Cases Stanley Cobb

7 (A guest will give a clinic at this time, the name will be announced later)

FRIDAY, APRIL 12, 1929

1 (A guest will give a clinic at this time, the name will be announced later)

2. Cases of Disease of the Hemopoietic System. Ralph C Larrabee.

3 Lymphoblastoma Demonstration of Cases Henry Jackson, Jr

4 Tropical Diseases Demonstration of Cases George C Shattuck.

5 Fluoroscopic Diagnosis in Chest Conditions Demonstration of Cases Harold W Dana

6 Carcinoma of the Head of the Pancreas Demonstration of Cases Irving J Walker

C

BOSTON CITY HOSPITAL  
THORNDIKE MEMORIAL LABORATORY

WEDNESDAY AND THURSDAY

APRIL 10 AND 11

BETWEEN 10 30 AND 12 30

Demonstration of Researches Concerning the Following Topics

Dr Castle and Associates

Dr Jackson and Associates

Dr Lawrence and Associates

Dr Lennox

Dr Minot and Associates

Dr Nye and Associates

Dr Wearn and Associates

Dr Weiss and Associates

Anemia

Malignant Tumors

The Physiology and Pathology of White Cells

Epilepsy

The Blood

Bacteriological Problems

The Capillaries

Vascular Problems

# BOSTON CITY HOSPITAL SOUTH DEPARTMENT

Program in charge of Edwin H. Place

Ward visits on (1) diphtheria, (2) scarlet fever, (3) a few of the other minor groups such as chicken pox, mumps, measles and whooping cough

Amphitheater demonstration of cases of chronic laryngeal injury and other damages resulting from contagious diseases

E

## BOSTON DISPENSARY

TUESDAY, APRIL 9, 1929

- |  |  |
|--|--|
| 1 Heart Disease David Davis            | 4 Chronic Pancreatic Disease Bert B Hershenson |
| 2 Essential Hypertonia David Ayman     | 5 Tuberculosis H Louis Kramer                  |
| 3 Neurological Clinic A Warren Stearns |  |

- 4 Obesity Mark Falcon-Lesses  
5 Gastro-Intestinal Clinic Percy B Davidson

THURSDAY, APRIL 11, 1929

- 1 Neurosyphilis Arthur Beck  
2 Neurasthenia Joseph H Kaplan  
3 Nephrosis Tobert W Buck  
4 Domiciliary Medicine in Clinical Teaching—Selected Case Osadore Olef  
5 Domiciliary Medicine in Clinical Teaching—Selected Case Charles Korb  
6 Diabetes James H Townsend

WEDNESDAY, APRIL 10, 1929

- 1 Bronchiectasis William Dameshek  
2 Psychalgia Joseph H Pratt  
3 Arthritis John D Adams

F

## CHILDREN'S HOSPITAL

Program in charge of Kenneth D. Blackfan

G

## HOMEOPATHIC HOSPITAL EVANS MEMORIAL CLINIC

TUESDAY, APRIL 9, 1929

- 1 Sterility Clinic Special Emphasis to be Placed on the Constitutional Factors in Sterility S R Meaker and A W Rowe

WEDNESDAY, APRIL 10, 1929

### Endocrine Clinic

- 1 Endocrine Diagnosis and Therapy Charles H Lawrence  
2 Endocrine Disorders Associated with Otosclerosis and the Meniere Syndrome D W Drury  
3 Eye Findings in Endocrine Disorders W D Rowland  
4 Cases Presenting Outward Evidence of Endocrine Disorders Found on Study not to have Endocrine Disturbance A W Rowe

- 5 Dementia Praecox L G Hoskins  
6 The Follicular Hormone J C Janney  
7 Discussion on Sugar Metabolism as Influenced by Insulin in Pituitary Disease H Ulrich and A W Rowe

THURSDAY, APRIL 11, 1929

### General Medical Clinic

- 1 Heart Clinic W D Reid  
2 Intestinal Migraine C W McClure  
3 Neurology N H Garrick  
4 Lung Abscess, Diagnosis and Treatment Bronchoscopy, the Use of the Bronchoscope in Diagnosis and Treatment. L R Johnson

FRIDAY, APRIL 12, 1929  
(Program to be announced later)

## H

## MASSACHUSETTS GENERAL HOSPITAL

- 1 Clinic by James E. Paullin, Atlanta
- 2 Thoracic Clinic Frederick T. Lord
3. Cases of Hypertension William B. Breed
4. Cardiac Clinic. Howard B. Sprague
- 5 Endocrine Clinic Walter Bauer and Dwight L. Sisco

WEDNESDAY, APRIL 10, 1929

- 1 Clinic by Lewellys F. Barker, Baltimore
- 2 Demonstration of Medical Cases William B. Robbins
- 3 Pediatric Clinic Fritz B. Talbot and Harold L. Higgins
4. Clinico-pathological conference. Richard C. Cabot and Tracy B. Mallory
- 5 Diabetic Clinic Roy R. Wheeler

THURSDAY, APRIL 11, 1929

- 1 Clinic by O. H. Perry Pepper, Philadelphia
- 2 Neurological Clinic James B. Ayer
- 3 Psychotherapy of Gastro-Intestinal Diseases William Herman
4. Gastro-Intestinal Clinic Chester M. Jones
- 5 Indications for Splenectomy Arlie V. Bock
- 6 Cases of Pernicious Anemia Wyman Richardson.

FRIDAY, APRIL 12, 1929

- 1 Clinic by J. C. Meakins, Montreal
- 2 Demonstration of Cases Gerald Blake.
- 3 Medical Clinic James H. Means
4. Demonstration of Cases F. Dennette Adams
- 5 Anaphylaxis Clinic Francis M. Rackemann

## I

## NEW ENGLAND BAPTIST HOSPITAL

Program in charge of Albert A. Hornor

## J

## NEW ENGLAND DEACONESS HOSPITAL

Program in charge of Elliott P. Joslin

- |   |  |
|---|--|
| <ol style="list-style-type: none"> <li>1 Carcinoma of the Colon and Colitis from the Surgical Point of View Daniel F. Jones</li> <li>2 Gastro-Intestinal Cases Sara M. Jordan and Chester Kiefer</li> <li>3 Thyroid Cases Frank H. Lahey</li> </ol> | <ol style="list-style-type: none"> <li>4 Pedigreed Diabetics Elliott P. Joslin</li> <li>5 Surgery in Diabetics L. S. McKittrick</li> <li>6 The Pathology of Diabetes Shields Warren</li> </ol> |
|---|--|

There will be further additions to this program including clinics by larynologists, ophthalmologists, gynecologists and roentgenologists

## K

## PETER BENT BRIGHAM HOSPITAL

- |  |   |
|--|---|
| <ol style="list-style-type: none"> <li>1 Diagnosis of Certain Forms of Heart Disease Lewis A. Conner, New York</li> <li>2 Chronic Myocardial Disease Henry A. Christian</li> <li>3 Results of Treatment of Duodenal Ulcer E. S. Emery</li> </ol> | <ol style="list-style-type: none"> <li>4. Some Considerations on the Relation of Cardio-Renal System to Surgery of the Urinary Organs William S. Quimby</li> <li>5. Bronchoscopy in Lung Disease Lyman C. Richards</li> </ol> |
|--|---|

WEDNESDAY, APRIL 10, 1929

1 Cardiac Disease, the Result of Infectious Processes James B Herrick, Chicago

2 Gallbladder Disease Channing Frothingham

3 Bronchial Asthma I Chandler Walker

4 Anemia William P Murphy

5 Thrombophlebitis John Homans

THURSDAY, APRIL 11, 1929

1 Mitral Stenosis David Riesman, Philadelphia

2 Signs of Persisting Infection in Acute Rheumatic Fever Clifford L Derick

3 Hemorrhagic Nephritis James P O'Hare

4 A Surgeon's Views of the Treatment of Peptic Ulcer David Cheever

5 Neurosurgical Conditions Harvey Cushing

FRIDAY, APRIL 12, 1929

1 Hypertension Charles F Martin, Montreal

2 Vascular Disease in Diabetes Mellitus Reginald Fitz

3 Treatment of Certain Types of Cardiac Arrhythmia. Samuel A Levine

4 Treatment of Trifacial Neuralgia Gilbert Horrax

5 Diuretics Henry A Christian

L

### ROBERT BRECK BRIGHAM HOSPITAL

Program in charge of Louis M Spears  
Clinics on Arthritis

M

### UNITED STATES NAVAL HOSPITAL

Program in charge of Capt F L Pleadwell, MC, U S N

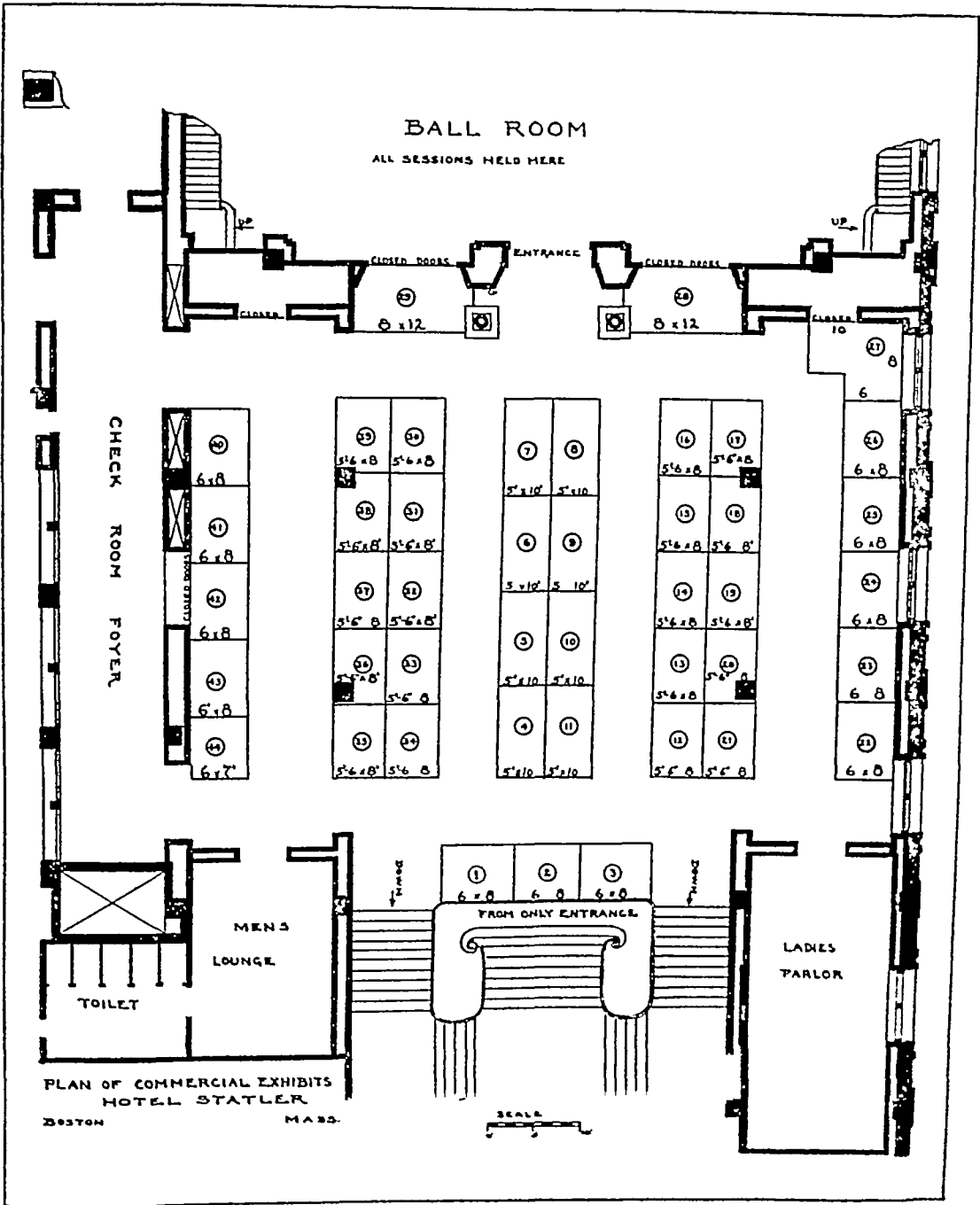
Presentation of medical cases in the conference room of the hospital each morning. Following this the group will be split up in sections of five. Each section will be in charge of a ward medical officer, and the balance of the morning will be devoted to ward rounds.

### TECHNICAL EXHIBIT

The technical exhibits have been arranged by the Executive Secretary, Mr E R Lovcland, and the following chart shows the arrangement of booths and the assignment to exhibitors from various parts of the country. The exhibits are highly diversified in their variety and will bring to the attendants at the Clinical Session, the latest and most improved equipment, the best pharmaceutical products, almost the whole library of medical publications and many other products of special interest to the Internist, Pediatrician, Neurologist, Psychiatrist, Radiologist and research worker.

This Exhibit is undoubtedly the best arranged and the most popular one that the College has yet had. The location is in the Ballroom Foyer where all attendants to the meeting will pass through the exhibits daily. The Joseph T Griffin Decorating Company, of Louisville, Kentucky, who installed the exhibits for the American Medical Association, the Southern Medical Association and many other prominent medical associations will be in charge of the booths and decorations.





## LIST OF EXHIBITORS

SPACE	NAME	CITY AND STATE	PRODUCT
20	Abbott Laboratories	North Chicago, Ill	Pharmaceutical Products
12 & 21	D Appleton & Company	New York, N Y	Medical Publications
31	The Battle Creek Food Company	Battle Creek, Mich	Health Foods
22	Bausch & Lomb Optical Co	Rochester, N Y	Microscopes, Photomicro & Projection Apparatus
40	P Blakiston's Son & Co	Philadelphia, Pa	Medical Publications
13	The Borden Sales Company, Inc	New York, N Y	Merrell Soule Infant Foods
26	Britesun, Inc	Chicago, Ill	Therapeutic Lamps
25	Cambridge Instrument Co, Inc	New York, N Y	Electrocardiographs & Accessories, and other Physiological Instruments
3	Cameron's Surgical Specialty Co	Chicago, Ill	Electro-Diagnostic Surgical & Dental Instruments
44	G W Carnrick Co	Newark, N J	Pharmaceutical Products
1	Warren E Collins, Inc.	Boston, Mass	Roth-Barach Oxygen Apparatus
14	F A Davis Company	Philadelphia, Pa	Medical Publications
16	Deshell Laboratories, Inc	Chicago, Ill	"Petrologar"
42 & 43	General X-Ray Company	Boston, Mass	"Morse" Wave Generator, GX-Galvane-Faradie Plate, Diathermy Apparatus, Electrodes
34	Paul B Hoeber, Inc	New York, N Y	Medical Publications
19	Horlick's Malted Milk Corporation	Racine, Wis	Malted Milk Products
17	Kalak Water Company, Inc	New York, N Y	Kalak Water
4	Charles B Knox Gelatine Co, Inc.	Johnstown, N Y	Knox Gelatine
15	Lavoris Chemical Company	Minneapolis, Minn	"Lavoris"
30	Lea & Febiger	Philadelphia, Pa	Medical Publications
9	J B Lippincott Company	Philadelphia, Pa.	Medical Publications

29	MacGregor Instrument Company	Needham, Mass	Vim Stainless Steel Needles, Vim Emerald Luer Syringes, Vim Surgical & Medical Specialties Medical Publications
8	The Macmillan Company	New York, N Y	Anaesthetic Apparatus, Laboratory Equipment, Diagnostic & Scientific Apparatus, Vaccines, Intravenous Products, Orthopedic Appliances & Supplies, Instruments for Operating Room, E F M Catgut
2	E F Mahady Company	Boston, Mass	Malpractice Insurance
18	The Medical Protective Company	Chicago, Ill	Mellin's Food
24	Mellin's Food Company	Boston, Mass	Pharmaceutical Products
38	Mcreek & Company, Inc	Rahway, N J	Pharmaceutical Products
23	The Wm S Merrell Company	Cincinnati, Ohio	Infant Foods
32 & 37	Merrill Soule Company	New York, N Y	Medical Publications
35	The C V Mosby Company	St Louis, Mo	Medical Publications
39	Thomas Nelson & Sons	New York, N Y	Cod Liver Oil
28	The L L Patch Company	Boston, Mass	"Helloglass"
6	Pittsburgh Plate Glass Co	Pittsburgh, Pa	Psyllium Seed & Acidophilus Products
7	Richards, Inc	Glenolden, Pa	Medical Publications
11	W B Saunders Company	Philadelphia, Pa	"Graphic" Metabolism Apparatus
27	Saunborn Company	Cambridge, Mass	Optical Instruments, Projection Apparatus, Laboratory Equipment
11	Spencer Lens Company	Boston, Mass	Cod Liver Oil
36	Tailby-Nason Company	Boston, Mass	Electrocardiograph & Quartz Lamps
5 & 10	Victor X-Ray Corporation	Chicago, Ill	Pharmaceutical Products
33	{ Wintthrop Chemical Company, Inc H A Metz Laboratories, Inc	New York, N Y	

## THE WM S MERRELL COMPANY

Booth 23

"One hundred years ago, William Stanley Merrell, opened an apothecary shop which was destined to become 'America's Pioneer Pharmaceutical House' Before the first rail road had been built, when traveling was a tedious and even hazardous undertaking, The Wm S Merrell Company had its inception

"The little retail business grew and prospered Dr Merrell was joined in his enterprise by his brother Ashbel and the firm became known as Wm S and A S Merrell Later the business developed into a wholesale, importing and manufacturing firm and was incorporated under the name of Wm. S Merrell and Company"

This is the history of the founding of the name of Wm S Merrell Company, an organization that has rapidly grown into one of the foremost pharmaceutical houses in America

"Definitely associated with the name of Merrell is the pioneer work on the *natural salicylates* In the present generation, the house has developed the detoxol products, which have contributed a new factor in preventive dentistry, *fibrogen*, the blood coagulant which has already won a place for itself in medicine, and but recently has perfected a new, palatable castor oil emulsion, *lacrism* That universal household remedy—castor oil—which up to the present time has been esteemed for its medicinal action and abhorred for its taste and odor, has in *lacrism* all the objectionable taste and odor removed, and the full therapeutic potency retained"

## KALAK WATER COMPANY

The Kalak Water Company will have an exhibit in the Exhibit Hall—Space No 17—where Kalak Water will be served, that all physicians visiting the booth may have an opportunity of tasting this highly palatable and agreeable alkaline water

Kalak Water is made of distilled water and chemically pure salts of the kind normally present in the body, is non-laxative and higher in available alkali and richer in Calcium than any natural or artificial water known

## DASHELL LABORATORIES, INC

—Petrolagar in Place of Mineral Oil—

The advantages of an emulsified mineral oil over plain liquid petrolatum are so manifest that clinicians everywhere are increasingly adopting Petrolagar for use routinely in the management of intestinal stasis

Petrolagar is a perfect emulsion of mineral oil with agar-agar, and for convenience is made in four types

Petrolagar—Plain, No 1, Blue Label, is the plain emulsion

Petrolagar, No 2, Red Label, contains  $\frac{2}{3}$  of a grain of phenolphthalein to the tablespoonful

Petrolagar, No 3, Green Label, is the emulsion combined with 8% milk of magnesia

Petrolagar, No 4, Brown Label, is the same as No 1 except that it contains no sugar

Petrolagar will be represented by an interesting exhibit at the forthcoming Clinical Session in Boston, Booth 16

## THE BATTLE CREEK FOOD COMPANY

The whole range of Breakfast Cereals, Beverages, Diabetic Foods, Confections, Sanitarium Crackers and Biscuits, new Meat Substitutes, Savita, Food Ferrin, and Food Accessories for Combating Constipation will be exhibited by The Battle Creek Food Company at Booth 31

"Healthful Living" contains fundamental facts about food and feeding, and may be secured from this Company upon request

## THE BORDEN SALES COMPANY, INC

At Exhibit Booth No 13, the Borden Sales Company will exhibit all types of concentrated forms of milk including condensed, evaporated and powdered milk. These will include Merrell-Soule Powdered Whole Lactic Milk, "Klim" and other products

The Borden Company is today the largest milk concern in the world. This Company, founded nearly three quarters of a century ago by Gail Borden, the inventor of the process for concentrated milk, now handles and distributes every milk product, including fluid milk, condensed milk, evaporated milk, powdered milk, malted milk, ice cream and cheese. Its markets are scattered throughout the world.

## LAMOTTE CHEMICAL PRODUCTS COMPANY

The LaMotte Chemical Products Company, Baltimore, Maryland, has engaged an exhibit booth at the entrance to the check room foyer, to be known as Booth No 45, and entire space will be confined to the showing of LaMotte Blood Chemistry outfits. These offer simplified blood chemistry methods for the general practitioner as well as for the technician, and were developed originally upon specific requests from their patrons. These outfits have become so popular that they have made them available to the medical profession in general. The outfits were developed in co-operation with eminent technicians in institutions where such research is carried on. In each case, the complete apparatus with reagents and complete instructions as a self contained unit are provided, and at a moderate price. At the Boston Clinical Session, they will exhibit the following:

LaMotte Blood Urea Outfit	LaMotte-Pigford Icterus Index Comparator
LaMotte Blood Sugar Outfit	LaMotte-Wuth Bromide Comparator
LaMotte Urine Sugar Outfit	LaMotte Blood pH Comparator
LaMotte Blood Calcium Outfit	LaMotte Urine pH Comparator

## BAUSCH &amp; LOMB OPTICAL COMPANY

Booth No 22

The emphasis which the World War laid on the medical laboratory, during the years of stress in which it was the scene of intensive research and practice in matters of diagnosis and treatment, developed the laboratory to a point where it is now considered indispensable to hospital practice. It was this emphasis that focused the attention of the American College of Physicians and the American College of Surgeons on the clinical laboratory, which factor is largely responsible for the present constructive interest in it.

A great deal of work coming within the scope of the hospital laboratory involves the use of optical instruments. Tests touching pathology, bacteriology, hematology, serology, immunology, chemistry, etc., and microscopical examinations of urine, blood, frozen sections, cerebra-spinal fluids, secretions and bacteria, require optical equipment of the highest quality and greatest accuracy.

The Bausch & Lomb Optical Company, whose Scientific Bureau has, in many instances, collaborated with such men as Dr G. Carl Huber of the University of Michigan, Dr Otto Folin of the Harvard Medical School, and others of like practical experience, are manufacturing a complete line of optical instruments for the medical laboratory. In view of the strides general science has made with the aid of optical instruments, it is fitting that the vast experience of this Company over a period of seventy-five years, through the medium of its products, should be placed at the service of the medical science. The full line of scientific instruments which the Bausch & Lomb Optical Company has especially designed for the medical profession will be on exhibit at Booth 22, Thirteenth Annual Clinical Session of The American College of Physicians, Boston, April 8-12, 1922.

## ELECTION TO FELLOWSHIP

BY THE

## BOARD OF REGENTS

NOVEMBER 17, 1928

Baldwin, William S	Lorain, Ohio	Shaw, Wm J	Rome, Ga
Bean, Leo C	Gallipolis, Ohio	Sheep, Maj Wm L	Washington, D C
Behlow, Lt Comdr William W		Shields, Maj Wm S	Denver, Colo
	Brooklyn, N Y	Tihen, Henry N	Wichita, Kansas
Bell, Maj Clarence R	Washington, D C	Traub, Hugo W	Chicago, Ill
Bierring, Walter L	Des Moines, Iowa	Vedder, Lt Col Edw B	
Blaisdell, Elton	Portland, Maine		Takoma Park, D C
Bloom, Charles J	New Orleans, La	Wallace, Louis O S	Kalamazoo, Mich.
Boardman, Walter W		Weiss, Soma	Boston, Mass
	San Francisco, Calif	Wesselhoeft, Conrad	Boston, Mass
Bogart, Franklin B	Chattanooga, Tenn	Westhoff, August W F	Brooklyn, N Y
Breed, William B	Boston, Mass	Whitaker, Paul F	Kinston, N C
Brereton, Gilbert E	Dallas, Texas	Wilson, John D	Scranton, Pa
Brooks, Clyde	University, Ala	Wohlrahe, Arthur A	Minneapolis, Minn.
Carr, B W	Washington, D C	Work, Philip W	Denver, Colo
Chambers, Lt Comdr John H			
	U S S Mercy, N Y		
Davis, Arthur E	Scranton, Pa		
DePew, Evarts V	San Antonio, Texas		
Ferguson, Donald R	Philadelphia, Pa		
Frank, Lorenz W	Denver, Colo		
Gasser, Lt. Comdr Rolland			
	Washington, D C		
Gauss, Harry	Denver, Colo		
Goldberg, Benjamin	Chicago, Ill		
Grabfield, G Philip	Boston, Mass		
Hall, Harry M	Wheeling, W Va		
Hall, Lynn T	Omaha, Nebr		
Henske, Joseph A	Omaha, Nebr		
Huston, John	Ann Arbor, Mich		
Inmon, Capt Ebner H	Washington, D C		
Jones, Austin B	Kansas City, Mo		
Jones, Chester M	Newton Center, Mass		
Kampmeier, Rudolph H	Ann Arbor, Mich		
Lee, Dee C	Hot Springs, Ark		
Lee, Roger I	Boston, Mass		
Lough, Walter G	New York, N Y		
McCorkle, Robert G	San Antonio, Texas		
Meyer, Julian E	Columbus, Nebr		
Meza, Ricardo Aquilar	Guatemala, C A		
Paulonis, Joseph F	Brooklyn, N Y		
Pratt, Comdr Lester L	San Pedro, Calif		
Reifenstein, Benedict W	Syracuse, N Y		
Riggs, Austen Fox	Stockbridge, Mass		
Rowland, Whitman	Memphis, Tenn		
Rupert, Mary P S	Philadelphia, Pa		
Sharp, Lt Comdr Elwood A			
	Pearl Harbor, Hawaii		

EXCERPTS—MEETING OF THE  
BOARD OF REGENTS  
OF THE  
AMERICAN COLLEGE OF  
PHYSICIANS

PHILADELPHIA, PA

NOVEMBER, 17, 1928

The meeting of the Board of Regents was called to order at The College Headquarters in Philadelphia at 10 30 A M, Saturday, November 17, 1928, by the President, Dr Charles F Martin of Montreal. Those present were Drs Aldred Scott Warthin, S Marx White, John H Musser, Clement R Jones, George Morris Piersol, Sydney R Miller, William Gerry Morgan, George E Brown, John A Lichty, Leonard M Murray, Alfred Stengel, James H Means, J C Meakins, James S McLester, John Phillips, Charles G Jennings, President Martin, and the Executive Secretary, Mr Loveland.

Among guests who were invited to meet with Committees, as members thereof, were the following Doctors William H Mercur, Roy R Snowden, B A Cohoe, Maurice Pincoffs, and W Blair Stewart.

Abstracts of the previous meeting were read by the Executive Secretary, complete Minutes having previously been placed in

the hands of all members of the Board, and upon motion regularly seconded and carried the Minutes were approved as read

Communications from absent Regents were reported after brief remarks by the President

The following gifts of publications to the College Library were reported

By Dr Edwin Henes, Jr (Fellow), October 3, 1928 1925, 1926 and 1927 volumes, Proceedings of the Inter-State Post-graduate Medical Association of North America

By Dr Philip B Matz (Fellow), October 23, 1928 Reprint, "Artificial Pneumothorax in the U S Veterans' Bureau"

By Dr Aaron E Parsonnet (Fellow), July 3, 1928 Reprint, "Abdominal Manifestations in Cardiovascular Diseases" Reprint, "Electrocardiographic Control of Active Digitalization in Auricular Fibrillation" Reprint, "Quinidin Therapy Uses and Contra-indications in Auricular Fibrillation"

By Dr M Lawrence Turner (Fellow), May 1, 1928 Book, "The Life of Pasteur," by Vallery-Radot Book, "Discovery, The Spirit and Service of Science," by Gregory Book, "Creative Chemistry," by Slosson Book, "The Riddle of the Rhine," by Victor Lefebure. Book, "The Future Independence and Progress of American Medicine in the Ages of Chemistry," by and through the Chemical Foundation

The following resolution was adopted

RESOLVED, to extend the thanks of the Regents to various donors of gifts, and stress the importance of sending books and literature only that are published by members of The College.

The following deaths were reported

Dr Henry G Brainerd, Los Angeles, Calif (Fellow), Dr Joseph Henry Byrne, New York, N Y (Fellow), Dr Ralph Campbell, Los Angeles, Calif (Fellow), Dr George P McNaughton, Detroit, Mich (Fellow), Dr S W Welch, Montgomery, Ala (Fellow)

The following resignations, after being individually considered, were accepted, with the recommendation that any who were delinquent at the time of submitting resignation should submit the delinquent dues

or be considered dropped from the membership list

Dr Wm. J Carson, Milwaukee, Wis (Fellow), Dr Wesley T Davison, Carmel, Calif (Fellow), Dr Louis Bertram Sachs, New York, N Y (Fellow), Dr George Harvey Agnew, Toronto, Ont. (Associate), Dr W P Millspaugh, Los Angeles, Calif (Associate), Dr Frank C Rote, Pittsburgh, Pa (Associate)

The Executive Secretary reported the offer of a gift of twenty-five hundred books through Colonel Percy M Ashburn (Fellow), of the Congressional Library, Washington After liberal discussion, it was decided that inasmuch as The College has limited accommodations for the storing of books and a questionable need for a general library, that it shall be the future policy of The College to accept only publications by members of The College, for those would serve as a valuable directory and possibly a memorial library of the members of this organization

The Executive Secretary was instructed to send an explanatory letter to Colonel Ashburn, the letter having been prepared by President Martin

After further discussion, the following resolution was adopted

RESOLVED, that the only library which this organization is endeavoring to gather shall be composed of publications by its own members,

An invitation from the Pan American Medical Association to attend their next Congress in Havana, December 29 to January 3, was read

The following Life Membership subscriptions were reported

Dr C F Martin, Montreal, Quebec, Can , Dr Carl R Comstock, Saratoga Springs, New York.

The following changes in status were reported

Dr Roland Davison from M C, U S A Service, Letterman General Hospital to Medical Director, Desert Sanatorium.

Dr Russell Pigford from full time teacher at Tulane to private practice at Tulsa, Okla

The following resolution was adopted upon motion by Dr. Warthin, seconded by Dr Stengel

RESOLVED, that a copy of *Annals of Internal Medicine* be sent to the British Museum each month and that no further complimentary subscriptions be entered except upon approval by the Board of Regents

Dr Alfred Stengel, Chairman of the Committee on *ANNALS OF CLINICAL MEDICINE*, submitted a full report dealing with the termination of the former publishing contract with the Williams & Wilkins Company, of Baltimore. The details of his report are printed elsewhere under "College News Notes" (December Number)

Editor Warthin pointed out that it would be desirable for him to index the new volumes of *Annals of Internal Medicine* under both an old series and a new series number, thus tying in the new journal with the first five volumes of *Annals of Clinical Medicine*

Dr Martin expressed the appreciation of the Regents to Dr Stengel and his Committee, Dr Jones, Dr Barker and Dr Piersol, for the labor that they have undertaken with regard to the bringing to a successful close the controversy with Williams & Wilkins

Under new business, the matter of Dr Mercur and his project for having The American College of Physicians appoint a committee to make a study of Groups and Clinics, with a view to formulating rules whereby The College will officially recognize such groups, was discussed. Dr Martin reported that Dr Mercur's Committee, consisting of Dr Mercur, Dr B A Cohoe, Dr Sydney R Miller, Dr Theodore R Squier and Dr R R Snowden, had met with a committee of the Board of Regents in which the subject of "Groups and Clinics" had been discussed and a recommendation in the way of a report from Dr Mercur filed. The plan proposed by Dr Mercur and his Committee provides that The American College of Physicians shall formulate a set of standards which shall cover groups and clinics

and shall initiate a plan whereby The College would accredit or approve those groups and clinics which meet the proposed standardization rules. Dr Mercur's final request was that the Regents appoint a committee to study further into the question in order that a definite conclusion might be submitted at a later meeting

Upon motion by Dr Warthin, seconded by Dr Stengel and regularly carried, the following resolution was adopted

RESOLVED, that a committee shall be formed, consisting of members of the Board of Regents, to thoroughly investigate the recommendations of Dr Mercur's Committee for accrediting groups and clinics, and report back at the next meeting of the Board of Regents at Boston

President Martin appointed the following to act on the Committee

Dr John H Musser  
Dr James McLester  
Dr Leonard M Murray

The Executive Secretary reported that although every effort had been made to collect delinquent dues during the past year, there are still outstanding fifty-three Fellowship dues delinquent for two years and forty-three Associateship dues delinquent for two years. The list of names was submitted to the Board of Regents and President Martin presented a draft of a proposed letter which he recommended be sent to the list. Upon motion by Dr Warthin, seconded by Dr Jones and regularly carried, it was resolved that the letter proposed be distributed to all such delinquent members

Dr James H Means, General Chairman of the Thirteenth Annual Clinical Session, reported in full upon the preparations for the Boston Clinical Session in 1929, presenting copy of the program in detail as arranged up to this time

Dr Warthin reported that many members have complained of too elementary clinics, and asked that every means be taken to see that speakers on the scientific program have their manuscript ready to hand to the re-



porter at the meeting. The Executive Secretary reported that all speakers are sent a marked program showing when and where they appear and also asking for an advance copy of the manuscript. Dr Warthin requested that the more important clinics be written up and Dr Means expressed a willingness to circularize the participants, stating that if they would care to write up their clinics, Dr Warthin will be glad to consider them for publication in *Annals of Internal Medicine*.

President Martin expressed the appreciation of the Board to Dr Means for taking so much care in the preparation of his advance program, and reported that Dr George Vincent of the Rockefeller Foundation has agreed to be a speaker at the Banquet.

The Executive Secretary, Mr Loveland, presented his report concerning the new headquarters of The College, the general activities of the business offices, membership activities, business preparations for the Clinical Session, promotion in advertising and circulation of *ANNALS OF INTERNAL MEDICINE*, and other matters concerning the business administration of The College.

Dr Warthin recommended that publishing organizations, whose books are reviewed in *Annals of International Medicine* be placed on the complimentary subscription list of the Journal. He further pointed out the success of his office and the Ann Arbor Press in bringing the Journal out on time and stated that it is his plan now to distribute the Journal on the fifteenth of each month. He expressed dissatisfaction with the advertising of the Smith, Kline and French Company in *Annals of Internal Medicine* and recommended that only "council approved" pharmaceutical products be accepted. He further suggested that advertising be restricted to sanatoria, publishing houses, instrument companies and manufacturers of "council approved" products.

Dr Charles G Jennings, Chairman of the Finance Committee, reported that the Executive Secretary had placed in his hands complete financial data for his Committee's consideration. The Committee's report, after due consideration, was as follows:

"In view of the present financial condition of The College, as reported by the Treasurer and the accounts of the Executive Secretary, and further in consideration of the immediate prospect of the adoption of changes in the Constitution and By-Laws, which will reduce the income from new members, it is deemed inadvisable at the present time to reduce either the initiation fee or the annual dues."

The report of the Committee on Finance was thereafter approved by the Board of Regents.

Dr Sidney R Miller, Chairman of the Committee on Constitution and By-Laws, presented mimeographed copies of the suggestions of his Committee. These were read and considered separately with suggested revisions, additions and assignments to Constitution or By-Laws being recommended.

The recommendations of the Board were referred back to the Committee on Constitution for a further rewriting of the proposed changes and the preparation of any other changes recommended in any part of the Constitution or By-Laws.

On motion by Dr Lichty, seconded, and regularly carried, the following resolution was adopted:

RESOLVED that the President shall send an explanatory note along with the final copy of proposed changes to the Constitution and By-Laws to each Fellow in order that members may more intelligently consider the proposed changes and cast their vote accordingly.

It was recommended that the Committee on Credentials and the Board of Regents meet a day in advance of the Boston Clinical Session in order to complete outstanding business and the election of applicants.

Dr George Morris Piersol, Chairman of the Committee on Credentials, presented the report of his Committee for disposal of applications for Fellowship, said report being unanimously adopted by the Board of Regents. (List of elections to Fellowship appears under "College News Notes" on another page.)

The following resolution was adopted: RESOLVED, that the present existing and

vertising contracts in ANNALS OF INTERNAL MEDICINE be observed, but hereafter no advertisement of articles not approved by the Council on Chemistry and Pharmacy shall be accepted

There was a general discussion concerning the eligibility of Anesthetists as a group for membership in The College. The Board ruled that Anesthetists are not considered eligible for membership in this organization.

General discussions concerning ritual, signing of the official roster, process of promotion of Associates to Fellows and other proposals for alteration of the Constitution and By-Laws were referred to the Committee on Constitution and By-Laws for further consideration.

Dr Stewart R Roberts (Fellow), Atlanta, Georgia, recently delivered a paper before the Third District Medical Society at Greenwood on "Nonvalvular Diseases of the Heart"

Dr George B Lawson (Fellow) was recently elected President of the Roanoke (Va) Academy of Medicine for 1929

Dr James J Waring (Fellow), Denver, was made President of the Colorado Society for Mental Hygiene at its recent organization

Dr Austin B Jones (Fellow), Kansas City, spoke before the Clay County Medical Society at Excelsior Springs, October 25, on "Diagnosis and Treatment of Auricular Fibrillation"

Dr Carl V Vischer (Fellow), Philadelphia, reported an interesting case of "Sarcomatosis," before the General Staff of the Hahnemann Hospital of Philadelphia on November 13th

Dr Daniel J McCarthy (Fellow), Philadelphia, addressed the Philadelphia County Medical Society, November 28, on "Nervous Diseases in Conjunction with Visceral Disorders"

Dr. Charles F Craig (Fellow), Lt Col MC, USA, addressed the Medical Officers of the District of Columbia recently on the Administrative and Professional Duties of Medical Officers

Dr Louis M Warfield (Fellow), Milwaukee, addressed the Chicago Society of Internal Medicine at its one hundredth regular meeting on November 26, on "Hypothyroidism"

"A Unified Plan of Tuberculosis Control" was the subject of Dr Benjamin Goldberg (Fellow) before the annual meeting of the New York Tuberculosis and Public Health Association on November 2

Col Bailey K Ashford, U S Army retired, represented the U S Army Medical Corps and the Government of Porto Rico as a delegate to the International Congress of Tropical Medicine and Hygiene at Cairo, Egypt, December 15-22

Dr Torald Sollmann (Fellow), Professor of Pharmacology and Materia Medica at Western Reserve University, Cleveland, Ohio, was appointed Dean of the School of Medicine of that institution by action of their trustees, following the resignation of Dr C A Hamann on November 14th. Dr Sollmann is an alumnus of Western Reserve University, and has been active on the faculty and various committees for several years. He is the author of many articles contributed to scientific journals and of text books. A recent text, of which Dr Sollmann is joint author with Dr Paul J Hanzlik, is "An Introduction to Experimental Pharmacology," published by the W B Saunders Company. Dr Sollmann is a member of the Council on Pharmacy and Chemistry of the American Medical Association, and a member of the Executive Committee of the United States Pharmacopeia.

The Pottenger Sanatorium, Monrovia, California, celebrated on December 5, 1928, the Twenty-fifth Anniversary of its opening. Ex-patients and many friends of the

institution attended a reception from eleven until two o'clock. At twelve o'clock, a buffet luncheon was served on the lawn, and in the evening, a dinner was given to former associates and assistants, members of the Trudeau Society and other local physicians. Dr F M Pottenger, F A C P, Medical Director of the Sanatorium, is to be congratulated upon the success of this institution.

Dr Alfred Stengel (Fellow), and Dr O H Perry Pepper (Fellow), both of Philadelphia, offered two postgraduate lectures on "Diseases of the Kidney" to a group of ninety physicians in Wilkes-Barre, Pa, during November.

At the Sixty-eighth Semi-annual Meeting of the Tennessee Medical Association at Columbia, November 22-23, Dr Jack Withersoon (Fellow), Nashville, discussed "Remote Causes of Disability," Dr J O Mainer (Fellow), Nashville, discussed "The Value of Rest and Exercise in the Treatment of Tuberculosis," and Dr W S Leathers (Fellow), Nashville, discussed "Public Health."

Dr Linn J Boyd (Fellow), New York, is Editor-in-chief of the Journal of the American Institute of Homeopathy.

Dr Carroll C Pounders (Fellow), Oklahoma City, was guest of honor and delivered a talk on "Pediatrics," illustrated by lantern slides, before the Okmulgee-Okfuskee Medical Societies at Henryetta, Oklahoma, on November 12.

Dr L J Moorman (Fellow), Oklahoma City, edits the section on Tuberculosis in the Journal of the Oklahoma State Medical Association. Dr Moorman conducts the Moorman Sanatoria for the treatment of Tuberculosis, in Oklahoma City.

Dr D E S Colman (Fellow), New York, is an Associate Editor of the Journal of the American Institute of Homeopathy.

Major articles have recently been contributed by Fellows of The College to The

Journal of the American Medical Association as follows:

Dr John A. Toomey, Cleveland  
"Treatment of Scarlet Fever by Specific Antitoxins and Serums"

Dr L R Sante, St Louis  
"Injuries to the Chest"

Dr McKim Marriott (with Dr A F Hartmann), St Louis  
"Newer Aspects of Acidosis"

Dr R S Boles (with J B Carnett), Philadelphia  
"Fallacies Concerning Chronic Appendicitis"

Dr Cyrus C Sturgis (with Dr Millard Smith), Ann Arbor  
"Pernicious Anemia"

Dr W W Duke, Kansas City  
"The Pollen Content of Still Air"

Dr Harry M Hall (Fellow), Wheeling, W Va, is President of the West Virginia Medical Association. He and Dr C A Ray (Fellow), Charleston, past President of the West Virginia Medical Association, delivered addresses, in connection with the School of Medicine program at the inauguration of Dr John Roscoe Turner as President of the University of West Virginia on November 28.

Dr John William Shuman (Fellow) and Dr Frederick Speik (Fellow), both of Los Angeles, addressed the Physicians and Surgeons of the South West at Albuquerque, November 9th, on "Lung Abscess" and "Associated Pathology of Gastric Ulcer," respectively.

Dr Hans Lissner (Fellow), San Francisco, at Richmond, California, on October 13th spoke before the Contra Costa Medical Society on "Goiter Survey of the High Schools of Contra Costa County."

Dr V M Longmire (Fellow) Temple, Texas, during October, addressed the Falls County Medical Society at Marlin on "Transfusions by the Citrate Method."

The November issue of the Journal of the American Institute of Homeopathy contained Articles by two members of The College as follows "A Consideration of Renal Glycosuria" by Dr E Roland Snader, Jr, (Fellow) and "Clinical Aspect of Massive Collapse of the Lung" by Dr Donald R Ferguson (Fellow), both of Philadelphia

Surgeon General E. R. Stutt (Fellow), U S Navy, was among the speakers at the Armistice dinner given by the Philadelphia County Medical Society on November 13

Dr Felix J Underwood (Fellow), Jackson, Mississippi, was elected a Vice President of the Southern Medical Association at Asheville, November 14

Dr James G Carr (Fellow) addressed the Annual All-Day Fall Clinical Meeting of the Adams County Medical Society at Quincy, Illinois, October 15, on "The Heart and the Electrocardiogram"

Dr Harold Swanberg (Fellow), Quincy, Illinois, is Editor of The Radiological Review and the Chicago Medical Recorder. On the Editorial Board of this journal appear also the names of Dr Leon T LeWald (Fellow), New York, Dr George E Pfahler (Fellow), Philadelphia, Dr Albert Soiland (Fellow), Los Angeles, and Dr I S Trostler (Fellow), Chicago

Dr J A Barga (Fellow), Rochester, Minnesota, spoke on "Etiology, Symptomatology and Medical Treatment of Chronic Ulcerative Colitis" before the Yorkville Medical Society on November 19

Dr E Bosworth McCready (Fellow), Pittsburgh, delivered a lecture entitled, "Word-Blindness in School Children and its Influence upon Education, as a Cause of Retardation and as a Contributing Factor in the Diagnosis of Mental Deficiency" before the Department of Special Sub-Normal Class Teachers of the New Jersey State Teachers Association in Atlantic City on November 12

Dr Solomon Strouse (Fellow), Chicago, and Dr Oliver P Kimball (Fellow), Cleveland, addressed the Chicago Medical Society, November 7, on the "Treatment of Goiter" and "Science and Safety of the Prevention of Goiter," respectively

Dr Orlando H Petty (Fellow), Philadelphia, addressed a Tuberculosis Conference at the Philadelphia County Medical Society on November 14, using as his subject, "Value of Health Examinations in Tuberculosis Prevention" Dr Petty is Professor, Diseases of Metabolism, Graduate School of Medicine of the University of Pennsylvania

Dr Albert Soiland (Fellow), Los Angeles, addressed a special public meeting under the auspices of the Los Angeles County Medical Association, November 8, on "Cancer"

Maud Slye, Ph D, who presented the results of her research at the New Orleans Clinical Session of The College, was another speaker

Dr Benjamin Hobson Frayser (Fellow), Ft Harrison, Montana, was elected President of the United States Veterans Bureau Medical Society at its meeting at Helena, Montana, in early November

Dr Ralph Pemberton (Fellow), Philadelphia, delivered the twentieth Mary Scott Newbold lecture before the Philadelphia College of Physicians, November 7, on "Arthritis"

Dr Pemberton also addressed the Northwestern Ohio District Medical Association at Lima recently on "The Control of Arthritis and Rheumatism"

Dr John B Youmans (Fellow), Nashville, and Dr Stewart R Roberts (Fellow), Atlanta, were speakers at the Second Council District Medical Society of Ohio at Dayton on September 24-28

Dr Lewellys F Baker (Fellow), Baltimore, delivered the oration in medicine at the Havana Congress of the Pan American

Medical Association at Havana, December 29th to January 3rd

Dr O H Perry Pepper (Fellow), Philadelphia, presented a clinic before the Fayette County Medical Society of Pennsylvania at the Uniontown Hospital, November 15

Dr Wm M Sheppe (Fellow), Wheeling, October 9, presented a paper on "Bronchial Asthma" before the Lewis County Medical Society of West Virginia

Dr Herman N Bundesen (Fellow), Chicago, was elected Coroner for Cook County on November 6. Dr Bundesen was formerly Chicago's health commissioner

Dr Bailey K Ashford (Fellow), Colonel, U S Army, retired, on November 16th spoke on "Sprue and the Relation of Its Anemia to Pernicious Anemia" before the University of Wisconsin Medical Society at Madison

Dr George Tryon Harding, Jr (Fellow), Columbus, Ohio, is second in three generations of physicians in his family by the name of George T Harding. His father, Dr George T Harding, Sr, was in practice up until about the middle of November, when he died suddenly while on a vacation

Dr George Tryon Harding, 3d, of Worthington, Ohio, is a son of Dr George Tryon Harding, Jr. Warren G Harding, late President of the United States, was a brother of Dr George Tryon Harding, Jr

Dr John H Musser (Fellow and President Elect), New Orleans, belongs to the six generations of physicians in the Musser family. Going back to the days of William Penn, we find that the first Musser to settle in this country received during the early part of the eighteenth century a "grant of land with the privilege of practicing medicine" in Lancaster County, Pennsylvania. Since that time, there have been six physicians in direct descent through the Musser family

Dr William S Thayer (Fellow), Baltimore, was recently awarded the degree of doctor honoris causa of the University of Paris. Dr Thayer is Professor Emeritus of Medicine at Johns Hopkins University, School of Medicine, and also an officer of the French Legion of Honor

Dr E S Lam (Fellow), Oklahoma City, addressed the Okmulgee-Okfuskee County Medical Society, October 8, on "External Markins of Drug Reactions"

Dr Karl Rothschild (Associate), New Brunswick, N J read a paper on "Metal Poisoning with Presentation of a Case of Encephalopathy Following Lead Poisoning of Fourteen Years Duration" before the Staff of St Peter's Hospital, New Brunswick

Dr Lea A Riely (Fellow), Professor of Medicine at the University of Oklahoma School of Medicine, Dr William Engelbach (Fellow), Professor of Medicine at the St Louis University School of Medicine, Dr Leonard G Rowntree (Fellow), Professor of Medicine at the University of Minnesota Postgraduate School of Medicine and Chief, Section of Internal Medicine, Mayo Clinic, and Dr William A Jenkins (Fellow), Clinical Professor of Medicine at the University of Louisville School of Medicine, were on the faculty of the School of Medicine and University Extension Division of the University of Kansas for a series of intensive medical courses in Internal Medicine and Diagnosis given at Lawrence, Kansas, November 26-30, inclusive

Dr James Gray Carr (Fellow) Chicago was recently made an honorary member of the Adams County (Illinois) Medical Society

Dr Harold Swanberg (Fellow) Quincy gave an address on "Radium" before the Quincy Exchange Club on October 20th

Dr George Morris Piersol (Fellow) Philadelphia, is co author with Dr M M

Rothman, of an article entitled, "Liver Function Tests" in the December 8 issue of The Journal of the American Medical Association. In the same issue Dr John P Schneider (Fellow), Minneapolis, is co-author with Dr James B Carey of an article entitled, "Achlorhydria," Dr T. H Coffen (Fellow), Portland, with Dr H P Rush of an article entitled "Acute Indigestion in Relation to Coronary Thrombosis," Dr E C Trash (Fellow), Atlanta, with Dr J C Massee of an article entitled, "Narcolepsy"

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Dr William W Herrick (Fellow), New York City, addressed the Medical Society of the County of Queens, November 29th, on "Medical Complications of Pregnancy"

Dr Herrick also delivered on December 7th before the New York Academy of Medicine an address entitled, "Certain Medical Complications of Pregnancy and Their Treatment"

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Dr Frederick G Banting (Fellow), Toronto, on October 30th delivered at the University of Edinburgh the Cameron lecture, "giving an historical account of the researches that led to the discovery of insulin"

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Dr Howard T Karsner (Fellow), Professor of Pathology at the Western Reserve University School of Medicine, addressed the Cleveland Academy of Medicine at its

November meeting on "Abortus Infections and Clinical Medicine"

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Dr Robert S Barghoff (Fellow) and Dr. Frederick Tice (Fellow), Chicago, were speakers at the meeting of the Illinois State Trudeau Society at Champaign on December 13th

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Dr William F Lorenz (Fellow), Madison, Professor of Neuro-psychiatry at the University of Wisconsin Medical School, recently addressed the Marathon County (Wisconsin) Medical Society on "Acute Encephalitis"

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Dr Robert M Moore (Fellow), Indianapolis, spoke before the Indianapolis Medical Society, November 13th, on heart failure

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Dr Andrew C Ivy (Fellow), Professor of Physiology and Pharmacology at the Northwestern University Medical School, addressed the Milwaukee Academy of Medicine, October 19th, on newer physiology of the gallbladder

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Dr Felix J Underwood (Fellow), Jackson, Mississippi, was elected President of the medical alumni of the University of Tennessee recently. Dr Underwood is State Health Officer for Mississippi

# Then and Now in Boston

*Where We Meet, April 8-12, 1929*

*This article is furnished by the Boston Chamber of Commerce  
and is intended to give our subscribers interesting facts  
about our Convention City for 1929*

When you go to Boston, whether it is a matter of business or pleasure, you are going to enjoy yourself. The city has developed tremendously as a commercial and social centre within the last decade. Everywhere there is evidence of a wholesome spirit of enterprise and helpful co-operation in the fields of finance and manufacturing.

If on pleasure bent you will find that Boston possesses more "atmosphere" than any city on the eastern seaboard. Its historic buildings, famed the world over, the many unchanged pre-revolutionary scenes within easy motoring distance, its vista of rock bound coast and rose grown country lanes, a magnificent park system, beautiful suburbs quickly reached by railroad train and trolley car and its famed New England hospitality awaken a thrill of interest in the mind of the visitor.

Boston Town, you will remember, is nearly 300 years old. For it was in 1630 when the "Governor and Company of Massachusetts Bay in New England" sent out the first group of colonists headed by John Winthrop and because the principal men of the colony had lived in Boston, England, the name naturally was selected for their new home in America. And Boston has never lost its colonial flavor. The North End, Beacon Hill, Faneuil Hall, the Old State House, King's Chapel—a hundred reminders still linger, reminiscent of the days before Lexington called the thirteen original colonies to arms.

The reputation which Boston has long possessed of having narrow and tortuous

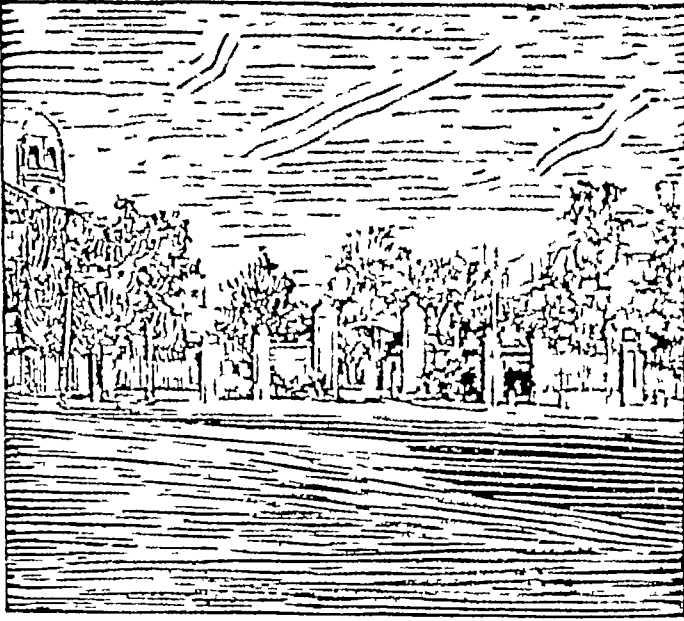
streets is no longer true. In the downtown district, streets are crooked, but Boston has grown from "downtown," as from a common center and Newer Boston has beautiful thoroughfares, wide and straight. Commonwealth Avenue is one of the finest streets in the United States, with its beautiful homes and delightful parkway construction.

Parts of Boston are still old and full of flavor, much of which has not been swept away by the growth of population and of commerce. One still finds many a monument of historic interest that calls to mind Colonial Days, although large areas once inhabited by the choice names of Boston's social and literary history have been completely rebuilt or changed because of demolition and by the great fire of 1872.

Boston is situated at the head of Massachusetts Bay, and is the terminal for steamship lines connecting with all ports of the world. Its railroad and trolley lines connect the city with every other community throughout New England. The city is the trading centre for the 4,500,000 people who live within a fifty-mile zone.

Boston is the business, industrial and population centre of New England—the latter being one of the richest industrial regions in the world. The real Boston extends far beyond the Municipal boundaries.

Boston has one of the finest natural harbors on the Atlantic Coast equipped with modern piers, docks and wharves. As a shipping point to commercial centres the city has a marked advantage over other



*Main Gate at Harvard University—Oldest of American Educational Institutions Established at Cambridge in 1636*

American seaports. It lies 200 miles nearer Europe than New York City, 1204 miles nearer Panama and the West Coast of South America than San Francisco, and 117 miles nearer Rio de Janeiro and Buenos Aires than Baltimore. As compared with any other American seaport, from 150 to 500 miles is saved by sailing from Boston to the ports of the United Kingdom, Continental Europe and the Near East.

Within easy distance of the city are many beaches, the Green and White mountain ranges with their magnificent scenery and grand views, woodlands and swift rivers, attractive in themselves, but especially appealing to hunters and

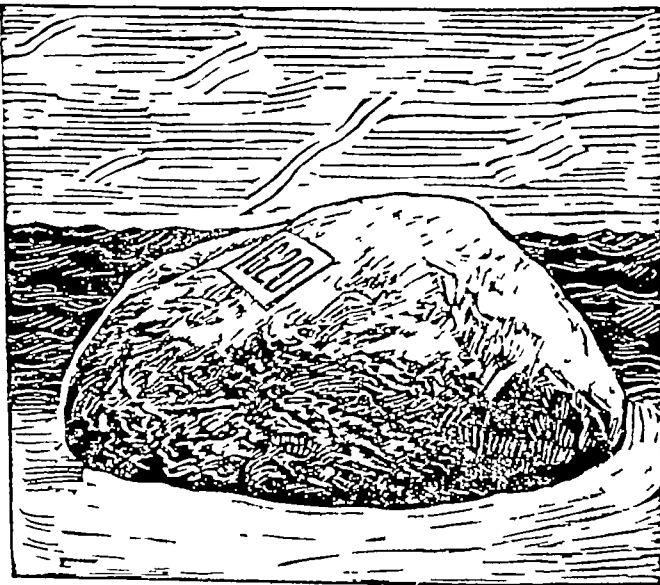
fishermen, pleasure trips by steamer around Massachusetts Bay or up and down the coast of New England, or the real joys of out-of-door sports of a New England winter. The hard-surfaced highways bring all of these attractions within easy reach of the city proper.

Metropolitan Boston is the shoe and leather centre of the world, the headquarters of cotton manufacturing, it is the greatest wool market of the United States, is the most up-to-date fish port of the world, and in production is exceeded only by Grimsby, England, and is one of the three great rubber manufacturing centres of America. High quality confectionery is Boston's fifth greatest industry.

The steam and electric railroad mileage alone of Metropolitan Boston is greater than that of any similar area in the Western Hemisphere, and serves a population of 1,772,000 people.

Boston is the natural radial point for the railroads of this section of the country and offers fast and frequent service to all parts of New England, to Canada, and West and South.

A unique example of co-operation between many municipalities which can scarcely be paralleled anywhere is offered in the Metropolitan Boston area. The Boston Metropolitan Park District comprises Boston and thirty-eight cities and towns within a radius of fifteen miles from



*Plymouth Rock, where the Pilgrim Fathers landed, "On a Stern and Rock-bound Coast," in 1620*



the State House, and consists of a chain of parks and boulevards which surprise the visitor by their extent and beauty

The Metropolitan Water Department furnishes water to all the cities and towns within the Metropolitan District, and the system is a commendable engineering feat. Water is brought from the Berkshire Hills in Western Massachusetts to the Wachusett Reservoir in Clinton, forty miles from Boston, and from there brought into the Metropolitan area by a chain of smaller reservoirs—a complicated engineering effort

The development of aviation finds Boston equipped with an admirably located

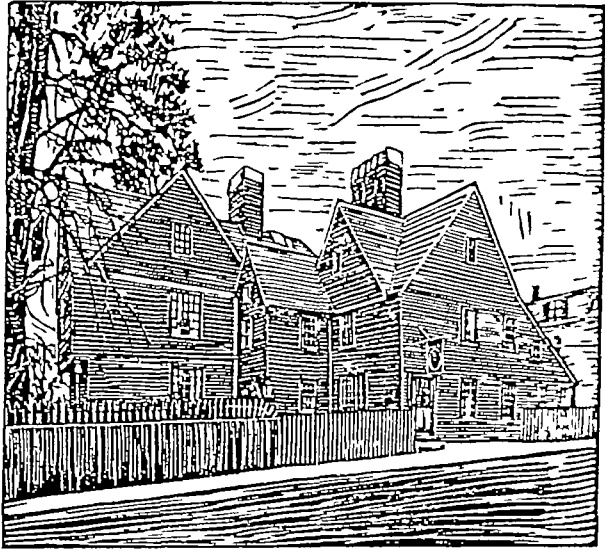
airport at Jeffries Point, less than two miles from the business centre of the city. Visiting pilots find there commercial hangar facilities. The landing field itself is unusually free from surrounding obstructions. It is used regularly by the Colonial Air Transport, which carries every day air mail from Boston to New York, the Boston Airport Corporation, the Regular Army, the National Guard and Reserve aviators.

A new airplane beacon light has been installed on the roof of a large department store as an aid to night flying.

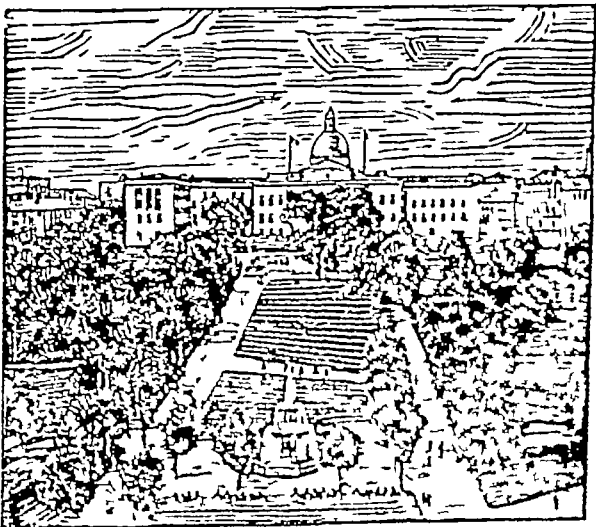
Boston is the first city in the world to inaugurate an all-day co-operative radio broadcast of news of interest to shoppers.

The theatres of Boston offer splendid opportunity to utilize their leisure time for entertainment and profit. Boston has ten "legitimate" theatres which bring to Boston the noted plays and the stage stars of the country. The city also has two-score moving picture houses, some of which are among the finest in the country.

Boston and New England are often called the "Birthplace of the American Nation," because of the historic richness of the region. In and around Boston are many places of attraction to every American who desires some time during his life to visit these historic shrines.



*House of Seven Gables—Salem. The original of Nathaniel Hawthorne's well known novel by that name*



*The Approach to the State House is one of the most beautiful scenes in Boston, viewed across the great expanse of Boston Harbour*



*Old North Church From its Belfry swung the lanterns which signalled to Paul Revere on the night of April 18 1775*

Space will not allow the enumeration of a complete list of these Yet there are certain of them that every visitor to the city ought to see

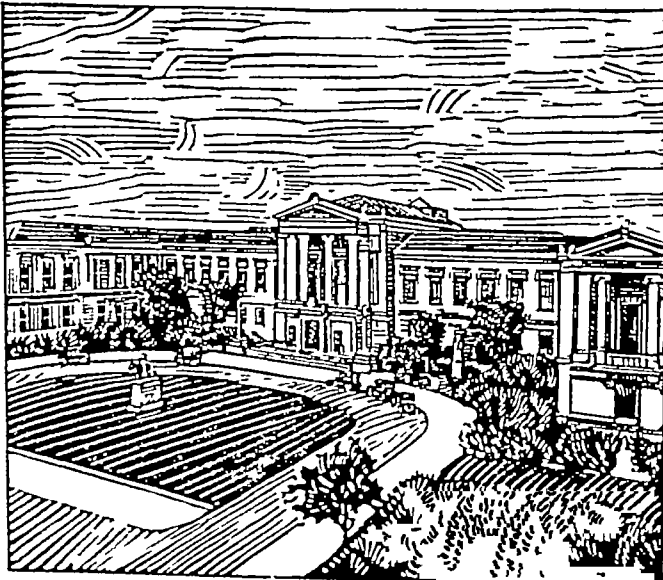
#### A FEW OF THE HISTORIC PLACES IN BOSTON

**BUNKER HILL MONUMENT**—Monument Square, Charlestown, commemorating the Battle of Bunker Hill, June 17, 1775. Winding stairway of 294 steps to top. Open 9 a. m. to 4 p. m. daily.

**BOSTON COMMON**—dates back to the beginning of Boston's history. It is situated in the heart of the city and is unique among Municipal public grounds. Its existence and pres-

ervation are due to the wise forethought of the first settlers. Four years after the settlement of the town it was laid out as "A place for a training field" and for "the feeding of cattell." A training field in part it has remained to the present day, and cattle did not cease to graze on it until the thirty's of the 19th Century. Every attempt to take away part of the land comprising the Common or the Boston Public Garden adjoining has determined resistance by the people of Boston.

**KING'S CHAPEL AND BURYING GROUND**—Tremont and School Streets. First built in 1686, present one in 1749. Old English architecture. First Episcopal church in New England. Here British officers worshipped during siege. Became First Unitarian church in United States, 1785. Open daily 9 a. m. to 4 p. m.



*1st Museum on Huntington Avenue—well worth a visit. Noteworthy on account of the Excellence of its Oriental Art objects.*

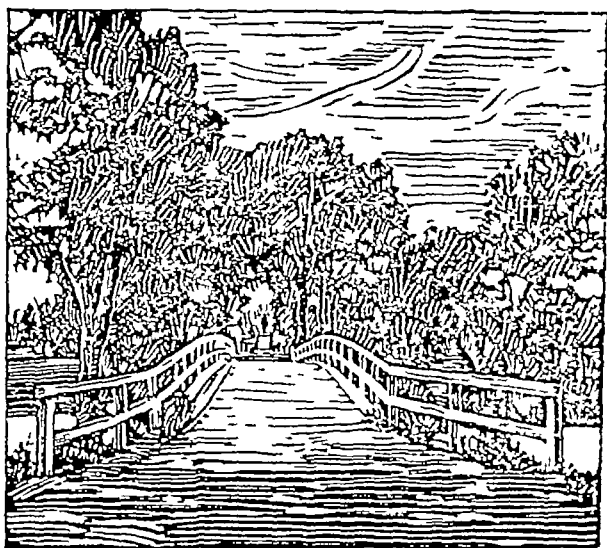
**OLD STATE HOUSE**—Washington Street, head of State Street. Here the first Town House was built, 1657. Burned in 1711. The present building was built in 1713. Here met colonial courts and legislatures, the town and city governments and the General Court of the Commonwealth. John Hancock was here inaugurated first governor of Massachusetts in 1780. In front of it occurred the Boston massacre. Here were the whipping post and the stocks. Open daily from 9 a. m. to 4 p. m.

**OLD GRANARY BURYING GROUND**—Tremont Street, between Beacon and Park. Here lie most of the personages of

historic Boston, seven early governors — Bellingham, Dummer, Hancock, Adams, Bowdoin, Eustis, Sumner, also Peter Faneuil, Paul Revere, the parents of Benjamin Franklin, the victims of the Boston Massacre, Robert Treat Paine, signer of the Declaration, John Phillips, first mayor of Boston, Elizabeth Goose ("Mother Goose") and many others. So called after 1737 from town granary on site of Park Street Church.

"OLD IRONSIDES"—(U S Frigate Constitution) launched at Boston in 1797, put into commission in 1798. Saw service in French War and War of 1812.

One of the first frigates authorized under the Constitution of the United States, marking the beginning of the U S Navy as it exists today. Frigate at Boston Navy Yard, Charlestown.



*Concord Bridge where was fired "The Shot Heard Round the World," in the memorable action, April 19, 1775*

FANEUIL HALL—Merchants Row and Faneuil Hall Square. "Cradle of Liberty." Built in 1742 by Peter Faneuil and given to Boston as a town hall. Burned in 1761, rebuilt 1763. Site of Revolutionary movement in Boston and the colonies. Enlarged 1805, from Charles Bulfinch's plans. Market below, public hall above, and armory of the Ancient and Honored Artillery Company (chartered 1638) over all. Open 9 a m to 5 p m daily.

BOSTON TEA PARTY TABLET—Atlantic Avenue at Pearl Street. Boston Tea Party. December 16, 1773.

BOSTON MASSACRE—At head of State Street, corner of Exchange Street. March 5, 1770, the first bloodshed in the American Revolution.

OLD NORTH CHURCH—Salem Street, foot of Hull Street, where on the evening of April 18, 1775, were hung the lanterns that gave warning of the British march on Concord and Lexington. Open 9 a m to 5 p m daily.

IN OR IN IMMEDIATE VICINITY OF BOSTON ARE THE HOMES OF Paul Revere, Harrison Gray Otis and two Presidents, John Adams and John Quincy Adams.

ALSO FOUR AMERICAN POETS. Henry Wadsworth Longfellow, Ralph Waldo Emerson, James Russell Lowell and Oliver Wendell Holmes.

## EDUCATION IN BOSTON

In New England were established the first free public schools maintained by taxation. The oldest American colleges are to be found in this region. Boston still is one of the first educational centres of the world.

In the Metropolitan Area are more than 200 universities, colleges, normal and technical schools, music and art institutions and private schools.

Among them are Harvard University, Massachusetts Institute of Technology, Boston University, Tufts College, Wellesley College, Radcliffe College, Simmons College, Boston College, the New England Conservatory of Music and Boston Normal Art School. The first five—among the ten largest educational institutions in New England—have a total registration of over 20,000 students.

## LIBRARIES

Metropolitan Boston contains 125 public libraries, with a total of nearly 3,000,000 books. Another 3,000,000 volumes are to be found in the colleges and special libraries.

Municipal Boston's world-renowned library at Copley Square with its thirty-one branches, has approximately 1,363,000 volumes and an annual circulation of about 3,400,000, more than two books apiece to every man, woman and child in its district. There is a library for each 24,000 of population.

## MUSIC IN BOSTON

New England Conservatory of Music

Boston Opera House

Symphony Hall, the home of the Boston Symphony Orchestra

## ART IN BOSTON

Museum of Fine Arts

Boston Public Library

Fogg Museum of Art Harvard University

Fenway Court (The Isabelle Stewart Gardner Museum)

## SOME PLACES OF GREAT HISTORIC INTEREST NEAR BOSTON

Not only is Metropolitan Boston rich in historic shrines, but the same is true of all New England. Within short distances of the city and easily accessible is historic—PLYMOUTH, where the Pilgrim Forefathers settled in 1620.

SCITUATE, OF "OLD OAKEN BUCKET" FAME

QUINCY, the birthplace of two presidents, John Adams and John Quincy Adams. Quincy also has the first incorporated railway in America, over which was hauled the granite for Bunker Hill Monument.

LEXINGTON, where the Minute Men defended American Liberty, April 19, 1775.

CONCORD, with its Sleepy Hollow Cemetery and the famous Bridge where was fired the shot heard round the world," April 19, 1775.

SALEM, where is the "House of Seven Gables" and the Hawthorne home.

PROVINCETOWN, where stands the Pilgrim Memorial Monument, commemorates the first landing of the Pilgrim Fathers.

SUDBURY, in this community is the famous "Wayside Inn," scene of Longfellow's "Pile of a Wayside Inn," built in 1686, and now owned by Henry Ford.

CAMBRIDGE, the home of Harvard University, the oldest college in America, Longfellow's House, and the site of the Washington Elm, under which tree Washington took command of the American Army, July 3, 1775.

FITCHBURG TO NORTH ADAMS, Old Mohawk Trail, "the pathway trodden by the Five Nations on their journeys from Hudson River to the Connecticut River."

BRATTLE, N. H., birthplace of Daniel Webster.

BRATTLE, Conn., famed for "Charter Oak." Table on which President Lincoln signed the Emancipation Proclamation is in the Connecticut State Library.

# The Pathology of Certain Signs and Symptoms in Primary Carcinoma of the Lung: Illustrative Cases\*

By CARL VERNON WILLER, M S, M D

**I**N one hundred clinical reports of carcinoma of the lungs (including the bronchi), selected at random from the literature, the various signs and symptoms were mentioned in diminishing order of frequency, as follows. Cough, sputum, usually bloody or blood-streaked at some time, but rarely of the "raspberry jelly" or 'currant jelly" type, pain in chest, dyspnoea, loss of weight, osteoarthropathy, usually in the form of clubbing of the fingers only, pleural effusion, frequently bloody, fever, venous engorgement, or oedema, or both, of the upper portion of the body, disturbances of the central nervous system, hoarseness, anorexia, paralysis of a vocal cord, dysphagia, nausea and vomiting, abdominal pain, inequality of the pupils, inequality of the radial pulses, pain in the arm, sense of pressure in chest, cachexia, cyanosis, pain in lower extremities, stertor, pain in back, headache, chills. In regard to relative frequency, cough is mentioned sixty-one times, the sputum forty-seven times, pain in the chest forty-four times and dyspnoea forty-four times in contrast to the last five items of the list which are each mentioned but once.

It is obvious that a compilation from so many different sources must not be accepted as dogmatically expressing the numerical importance of the various elements in the symptomatology of carcinoma of the lungs and bronchi. Many of the case reports which were used make no pretence of presenting the complete clinical picture. Nevertheless, the list does reveal the manifestations, both subjective and objective, which have been noted in connection with this disease condition and upon which a correct diagnosis was based in some instances, suspected in others, and entirely missed in a group which was altogether too large.

An extensive survey of the literature of primary carcinoma of the lungs and bronchi sustains the belief that the chief cause of inability to diagnose this condition correctly has been failure to keep it constantly in mind in differentiating chest conditions. The belief still held by many that primary carcinoma of the lung is an exceedingly rare condition not to be encountered in a large number

\*From the Department of Pathology, University of Michigan, Ann Arbor, Michigan.

ordinary medical practice, is to blame for this unconscious exclusion. When it is realized that at the present time, in Europe and in America, primary carcinoma of the lungs and bronchi is found once in every 200 autopsies upon adults and once in every twenty deaths from carcinoma (1), its importance will be appreciated and the possibility of its being present will always be entertained, especially if the patient be a male (74 per cent of all cases) in the fifth, sixth or seventh decades of life.

Inspection of the list of signs and symptoms gathered from the 100 random case reports of carcinoma of the lung shows that those near the head of the list are such as are of evident relationship to the primary lesion in the respiratory tract. Those near the foot of the list have a less obvious connection, some of them being secondary or indirect effects. If those cases are studied in which the diagnosis is not made until autopsy, it will be found that many of them have shown as important presenting signs and symptoms one or more of those which are relatively rarely mentioned in clinical case reports. It is especially important, therefore, to call attention to the occurrence of these more remote effects. This will be done by presenting the histories of twelve cases of primary carcinoma of the lungs and bronchi in which diagnosis was confirmed or established by autopsy in the Department of Pathology of the University of Michigan. Only one (2) of these cases (No. 1) has been published previously. The pathological basis for the signs and symptoms which suggested carcinoma

of the lungs, or should have done so in the undiagnosed cases, will be described in so far as it was ascertainable.

Physical findings are not included in the above list. They are oftentimes of great importance but usually change so decidedly in the course of the disease that they do not lend themselves well to analysis. The increasing area of dulness corresponding to the neoplasm itself, is a practically constant finding in the more advanced cases but the lung parenchyma peripheral to a carcinoma at the hilus may give a great variety of signs depending upon whether atelectasis, bronchiectasis, chronic fibroid pneumonia, neoplastic infiltration or surrounding pleural effusion is the determining factor.

It must be understood that the use or neglect of the two greatest aids in the diagnosis of primary malignancy of the lung is not primarily under discussion here. These are *bronchoscopy* (3) for direct inspection and probatory excision, and *roentgenoscopy* (4), particularly with the use of special means to aid visualization (pneumothorax, lipiodol, iodipin). Upon these two procedures much dependence must be placed in making a positive diagnosis. Neither of these, however, is to be entered upon lightly. It is now well recognized that lipiodol may remain for weeks or months in the bronchioles and alveoli and give rise to a foreign body reaction. Aortic aneurism, in particular, is an important contra-indication to bronchoscopy and should be ruled out by every possible means (3). Signs and symptoms must be present in a kind and to a degree which raises a strong pre-

sumption of malignancy or other grave pathology before these measures are utilized

Review of the list of signs and symptoms given above will show that there is not one of them which, taken alone, is pathognostic of primary malignant disease of the lung. They may be considered as indicating roughly four groups of pathological processes

1 Signs and symptoms due chiefly to local primary pathology

Cough  
Pain in chest  
Sputum  
Dyspnoea  
Cyanosis  
Dysphagia  
Stertor  
Effusion

2 Signs and symptoms of mediastinal tumor

Cough  
Pain in chest  
Dyspnoea  
Cyanosis  
Venous engorgement and oedema of the upper part of the body  
Recurrent laryngeal paralysis  
Hoarseness  
Inequality of pupils  
Inequality of radial pulses  
Abdominal pain  
Dysphagia  
Stertor

3 General systemic effects

Loss of weight  
Weakness  
Osteo-arthritis (clubbing of fingers)  
Fever  
Chills

Cachexia

Anorexia

Nausea and vomiting

4 Signs and symptoms frequently associated with metastasis

Evidence of central nervous system lesions  
Pain in lower extremities  
Pain in back  
Abdominal pain  
Headache

Of the twelve cases reported here four only were correctly diagnosed during life, although one other was considered to be intrathoracic malignancy, probably lymphosarcoma, and two were diagnosed as abdominal malignancy. It must be recalled that this series of cases begins in 1911. There has been a noticeable improvement in ability to diagnose primary carcinoma of the lungs and bronchi since that time. This is apparent in the abundant literature which has accumulated as well as in our local experience. In part, this gratifying improvement has been due to the more general clinical awareness of the relative frequency of the condition in question, and in part to the perfection and application of the special methods of investigation and confirmation to which reference has already been made. One can conclude that the successful *intra vitam* diagnosis of this condition involves a sequence of three steps: (1) The more or less constant inclusion of this condition in the list to be differentiated when obscure pathological conditions in the adult are being differentiated, (2) the recognition of certain signs and symptoms which raise such a strong pre-

sumption in favor of the diagnosis, that (c) special investigations are carried out which strongly support or confirm the diagnosis. The pathological processes producing the signs and symptoms entering into the second step form the basis of this study. In reviewing the following cases an attempt will be made, through the correlation of the pathological changes found at autopsy with the presenting signs and symptoms, to ascertain what opportunity, if any, of arriving at a correct diagnosis was offered. This is done without any intention of implying that a correct diagnosis *should* have been made in any particular case. Diagnosis by retrospection is notoriously easy and the advantage gained by the backward look has become proverbial.

#### CASE I

##### COMA, CYANOSIS, DYSPNEA

*Clinical Abstract* (5) An awning-maker, 47 years old, was brought to the hospital in coma. Only a meager history could be obtained from the patient's friends. For two years he had not been as well as formerly and had had marked dyspnea for some time, with epistaxis and hemoptysis. The patient had believed that he had asthma, and stramonium leaves were found in his pockets. He had slipped to the floor, unconscious, while seated in a chair in a hotel lobby.

Examination in the Department of Internal Medicine showed the patient to be intensely cyanotic, the skin dry, and the pupils evenly and markedly contracted, reacting but very little to light. There was marked dyspnea with great activity of the accessory muscles, and respiration was characterized by a short deep inspiration and long expiratory period. The rate was but 10 to 12 per minute. There were many inspiratory râles. No area of dullness was detected. The patient moved both arms but no spontaneous movements of the legs were

noted. The rectal temperature was 97.8° and 96° F.

Upon these findings a tentative diagnosis of morphin poisoning was made and treatment instituted accordingly. (Subsequent examination of the stomach washings showed no morphin.) Oxygen was used in an attempt to relieve the cyanosis and dyspnea, but without effect. The patient died four hours after entering the hospital.

*Autopsy* (A-352) No free gas or fluid was found in the pleural cavities. There were a few pleural adhesions, most marked at the right apex. The anterior border of the left lung reached the left parasternal line. The large bronchi of this lung were filled with creamy pus. The bronchial nodes on the left were small, heavily pigmented and showed no neoplasm. The anterior border of the right lung reached the right parasternal line. This lung was firmly bound to a tumor mass the size of an orange which included the right bronchial nodes, the esophagus and the descending aorta. This tumor mass completely surrounded the main bronchus to the right lung and the bronchial wall was infiltrated and destroyed. At this point the lumen of the bronchus was markedly narrowed. At the level of the bifurcation, the trachea showed a nearly complete stenosis, admitting only a 2 mm rod. This stenosis was due to the neoplasm mass compressing and infiltrating the trachea from without. Aside from the regional lymph nodes the only metastases found were in the left kidney. Microscopical examination showed the neoplasm to be a mucin-producing cylindric-celled adenocarcinoma.

*Pathological Diagnosis* Stenosing primary adenocarcinoma of right main bronchus. Metastases in bronchial lymph nodes and left kidney. Acute stenosis of trachea. Partial stricture of esophagus. Chronic purulent fibroid pneumonia. Bronchiectasis. Emphysema. Chronic leptomeningitis. Atrophy with acute and chronic passive congestion of all organs.

*Comment* In this instance there was no opportunity for detailed clinical



ical study The presence of pinpoint pupils led to a strong suspicion of morphinism and emergency treatment for that possibility was indicated Autopsy showed that death was due to asphyxiation from stenosis of the right main bronchus by neoplastic infiltration, and of the trachea, by neoplastic compression The coma cyanosis and dyspnea, which were the other important signs and symptoms, thus found their explanation It is probable that the contraction of the pupils was due to lesion of the sympathetic chain by the infiltrating new growth, although it is extremely rare for the pupillary change to be bilaterally symmetrical Survey of the case in retrospect shows a history of ill health for two years, dyspnea and hemoptysis, then extreme cyanosis, pupillary changes and coma from acute asphyxiation as the signs and symptoms The clinical manifestations are thus seen to be in accord with those listed above The nearly complete obliteration of the trachea explained the lack of clinical improvement when oxygen was administered

## CASE 2

### ABDOMINAL PAIN

*Clinical Abstract* A man, 57 years of age, giving his occupation as "bridgeman," first entered the Department of Dermatology and Syphilology complaining of sharp, intermittent pain in the upper left abdominal quadrant The pain was worse when lying down and had no relation to the taking of food There had been no nausea or vomiting The patient was believed to have required both gonorrhea and syphilis twelve years before, but a course of arsenphenamin treatment failed to influence the pain favorably and the patient continued to lose weight Physical examination did not show

evidence of disease of the thoracic organs Because of the location of the pain, constipation, a history of blood in the stools and X-ray evidence of some obstruction of the colon in the region of the splenic flexure when examined after a barium enema, the patient was transferred to Surgery where a diagnosis of carcinoma of the splenic flexure was accepted Laparotomy was done and the colon was found to be moderately constricted by firm fibrous adhesions These were cut There was no neoplasm

The patient was discharged from the Hospital about three weeks after this operation, still complaining of pain in the upper left quadrant and 'weakness' of the back At home the pain grew worse and he continued to lose weight, so he returned to the Hospital after 15 days A gently rounded swelling was now found over the left half of the back, extending from the fifth to the eighth rib This gave the first indication of intra-thoracic pathology Examination in the Department of Roentgenology showed the left half of the thorax to be everywhere more dense than the corresponding areas upon the right The greatest density occurred at the level of the ninth and tenth ribs posteriorly and in this region the shadow of these ribs could not be made out There was increased density of the hilus also Neoplasm of the thoracic wall was diagnosed The tumor mass on the back increased in size rapidly and the patient died 12 days after his second admission and 14 months after the onset of his illness

*Autopsy* (A-1140) Externally the body showed a large subcutaneous mass, located over, and apparently involving the left posterior portions of the fifth to eighth ribs This area showed no ulceration and the skin moved freely over the mass The laparotomy wound was represented by a well-healed scar The left lung was found to be heavily infiltrated at the hilus by a new growth which extended posteriorly and laterally to the thoracic wall where the lung was firmly adherent The fifth to eighth ribs in this region were extensively infiltrated by the neoplasm and showed several fractures Multiple metastases were

found as listed in the dictum which follows.

*Pathological Diagnosis.* Primary adenocarcinoma of bronchus of third order to lower lobe of left lung with direct extension through thoracic wall. Multiple metastases in lungs, bronchial and prevertebral lymph nodes, pleura, diaphragm, pericardium of ribs, heart muscle, liver, kidneys, pleura and retroperitoneal nodes. Bronchiectasis. Emphysema. Purulent lobular pneumonia. Hemorrhagic infarct of lungs. Fatty heart. Atherosclerosis of aorta. Brown atrophy of liver. Passive congestion and parenchymatous degeneration of all organs. Completely healed laparotomy scar.

*Comment.* This case is typical for that group of primary carcinomas of the lungs and bronchi in which attention is focused upon the abdomen because of referred pain. In this instance the pain seems to have been due to the direct extension of the neoplasm into, and finally through, the thoracic wall. Only with the appearance of the sub-cutaneous neoplasm in the left back was X-ray examination of the lung fields done. Earlier utilization of this aid would have forestalled the laparotomy which was unnecessary, for the pain in the upper left quadrant was entirely independent of the adhesions which were freed at that operation.

### CASE 3

#### VOMITING, ABDOMINAL PAIN, LOSS OF WEIGHT

*Clinical Abstract.* Clinical information is incomplete in regard to this case. The patient was a coal miner, 67 years of age, who entered the Department of Internal Medicine complaining of vomiting, abdominal pain and loss of weight. There was marked enlargement of the liver and some dysphagia. A diagnosis of abdominal malignancy, either of the cardiac end of the

*Autopsy.* (A-11622) External examination of the body showed an enlarged lymph node at the base of the neck on the left side. The left pleural cavity contained a large amount of bloody fluid. The pericardial sac was infiltrated on the mediastinal side by a neoplasm which extended into the wall of the auricle. The left lung grossly showed no neoplasm except a pleural plaque near the hilus. The roof of the right lung was occupied by a large mass which extended particularly along the main bronchus to the lower lobe. This bronchus was infiltrated and compressed by the surrounding neoplasm so that its lumen was completely obliterated for some distance. The pleura on the right side showed many nodules of new growth. About 4.5 cms below the level of the tracheal bifurcation the wall of the esophagus was infiltrated from without and at this point the lumen was distorted and there was a small traction diverticulum. The liver showed numerous metastases up to 3 cms in diameter.

*Pathological Diagnosis.* Primary medullary carcinoma of main bronchus to lower lobe of right lung. Metastatic carcinomatosis of both lungs, bronchial nodes and mediastinum with extension to pericardium and to wall of esophagus. Traction diverticulum of esophagus. Metastases in liver, retroperitoneal and left cervical nodes. Anthraxosis. Bronchiectasis. Chronic purulent bronchitis. Pulmonary infarction with beginning gangrene. Bronchopneumonia. Emphysema. Edema and passive congestion of the lungs. Brown atrophy of heart. Old syphilitic myocarditis of left ventricle. Sclerosis of coronaries and aortic cusps. Chronic passive congestion, atrophy and parenchymatous degeneration of all organs. Aortic atherosclerosis upon a syphilitic basis. Left-sided pyelonephrosis with nephrolithiasis. Dilatation of left ureter. Chronic pyelitis, ureteritis, cystitis and prostatitis. Orchitis fibrosa syphilitica. Lipoidosis of adrenals. Multiple anomalies of ribs.

*Comment* As in the preceding case the clinical manifestations led to a diagnosis of abdominal malignancy. Compression, distortion and traction diverticulum of the lower esophagus, together with liver metastases provided the anatomical basis inducing this incorrect interpretation. A "sentinel" node above the inner third of the left clavicle seemed to confirm this opinion. It must be remembered that carcinoma of the lung also frequently shows early metastasis by way of the ascending lymphatic trunks. This case closely resembles the third one in the series reported by Barron (6). A male patient, 52 years old, had as his only clinical findings pain in the stomach, anorexia, vomiting after each meal and loss of weight and strength. At autopsy an adenocarcinoma was found at the hilus of the right lung and there were metastases in the brain. Such patients frequently are asked to submit to laparotomy and the diagnosis may never be cleared up without autopsy.

#### CASE 4

##### PAIN IN LEGS

*Clinical Abstract* A farmer, 40 years old, entered the Neurology Service of the University Hospital because of pains in the legs. This symptom began ten months before entrance and gradually became unbearable. He had been taking as much as three grains of morphin sulphate at a dose in order to get partial relief. There had been some pain in the lower back also, but this was of minor importance to the patient. During the past three weeks first the left leg and then the right had become edematous. There had been neither dyspnoea nor hemoptysis at any time. X-ray examination gave positive evidence of malignancy of the left lung and a diagnosis of carcinoma of the lung with metastases to the spine was

made. At the insistence of the patient that something be done to relieve the pain in his legs he was transferred to Surgery for anterolateral chordotomy. Following the operation, which accomplished this purpose pain in the upper abdomen and chest became more severe, external dorsal decubitus developed and the patient died five weeks after the operation, and approximately one year after the onset of the pain.

*Autopsy* (A-1500) Externally the body showed the well-healed scar of a surgical incision extending 13 cms downward from the base of the neck, the site of the chordotomy operation. All of the bony prominences on the dorsal surface of the body were marked by areas of decubitus; the largest of these, over the sacrum, measuring 12 by 18 cms. The left lung was firmly adherent over its upper one-third. In the adhesions and in the free pleura of the lower portion of the lung there were numerous nodules of neoplasm. The bronchus to the upper lobe was occluded by a mass of neoplasm which infiltrated its wall and extended peripherally in the peribronchial tissue. The remainder of the lung contained many smaller neoplastic masses which were confluent in the upper lobe but discrete toward the base. Neoplasm was not found, either macroscopically or microscopically, in the vertebrae. The prevertebral retroperitoneal lymph nodes contained many metastases, even as low as in the lumbar region. Some of these large nodes lay in contact with and pressing upon branches of the lumbosacral plexus. There was no neoplastic infiltration of the spinal meninges or of the cord itself at the levels which were examined microscopically.

*Pathological Diagnosis* Primary medullary mucoid adenocarcinoma of bronchus to upper lobe of left lung. Stenosis of bronchus. Infiltration and lymphogenous metastasis throughout the left lung. Metastases in bronchial, mediastinal, lower cervical, prevertebral and retroperitoneal lymph nodes, right lung and liver. Septicopyemia. Multiple abscesses in lungs with gangrene and purulent pneumonia. Multiple abscesses in kidneys with metastatic descending necrotic

pyelonephritis, ureteritis, cystitis and urethritis. Terminal infection secondary to thoracic chordotomy. Thrombosis of pulmonary vessels, vena cava, external and internal iliac veins and vesical plexus. Anemic infarcts in kidneys. Congestion and edema of lower extremities. Relative tricuspid and pulmonary insufficiency. Passive congestion, atrophy and parenchymatous degeneration of all organs. Serous atrophy of all adipose tissue. Colloid goiter. Old orchitis.

*Comment.* Pain in the legs dominated the entire clinical picture of this case. X-ray examination of the chest revealed the primary source of the neoplasm which had never produced immediate signs or symptoms. That the pain in the legs was due to vertebral metastases was a clinical inference unsupported by evidence of a destructive lesion. There had been no evidence of a compression myelitis and microscopical examination of the vertebrae showed them to be free from neoplasm. Lymphogenous metastases among the nerves forming the lumbosacral plexus furnished the anatomical basis for an explanation of the pain. Edema of the legs was associated with thrombosis of the iliac veins. At the time of death this process had ascended for some distance in the inferior vena cava. Venous obstruction from the enlarged nodes filled with neoplasm made this thrombosis possible.

#### CASE 5

#### ENGORGEMENT OF SUPERFICIAL VEINS, HOARSENESS

*Clinical Abstract.* A farmer, age 56, was admitted to the Department of Internal Medicine of the University Hospital with his chief complaints swelling of the neck, difficulty in swallowing and pain in the back. He stated that his trouble began

three months before with hoarseness which was soon followed by swelling of the right side of the neck. He experienced greater difficulty in swallowing liquids than solids. Later dyspnea and a dry cough developed. He had not had hemoptysis. For two weeks there had been some impairment of vision in the right eye. Examination showed a scar on the upper left thorax anteriorly, extending over the shoulder, the site of an accidental wound with an ax. There was a marked distension of the veins of the neck and the superficial veins of the front of the chest and upper half of the abdomen. (See Figure 1.) The superficial venules were dilated along the line of the insertion of the diaphragm. There was marked dullness over the right chest from the second interspace up. The cervical glands were enlarged and hard on the right, a nodular mass filling the supraclavicular fossa, much less so on the left. The right arm was edematous. The Department of Otology reported a bilateral recurrent laryngeal paralysis. X-ray examination showed a very high diaphragm on the right, widening of the mediastinal shadow and haziness of the right apex. (See Figure 2.) A diagnosis of mediastinal tumor, probably lymphosarcoma, with mechanical obstruction of the superior vena cava, was made. The masses in the neck and the mediastinum were treated with X-rays without any relief. The difficulty in swallowing increased and the superficial venous engorgement became more marked. Death occurred eighteen days after admission.

*Autopsy (A-1760).* The brain showed a tumor mass in the right choroid plexus. The right pleural cavity contained 1500 cc. of yellowish fluid without evidence of blood. On the left, 900 cc. of similar fluid was found. The upper portion of the mediastinum was filled with a firm nodular neoplasm which extended especially toward the right along and above the clavicle and the first rib. At the base of the heart in the pericardial reflexions about the great vessels several small nodules were found. To the naked eye, there was no neoplasm in the left lung. The right lung, how



FIGURE 1 Case 5 Engorgement of the veins of the neck and of the superficial veins of the thorax and upper abdomen. Collateral venous circulation produced by compression of the superior vena cava and thrombosis of the right innominate and subclavian veins.

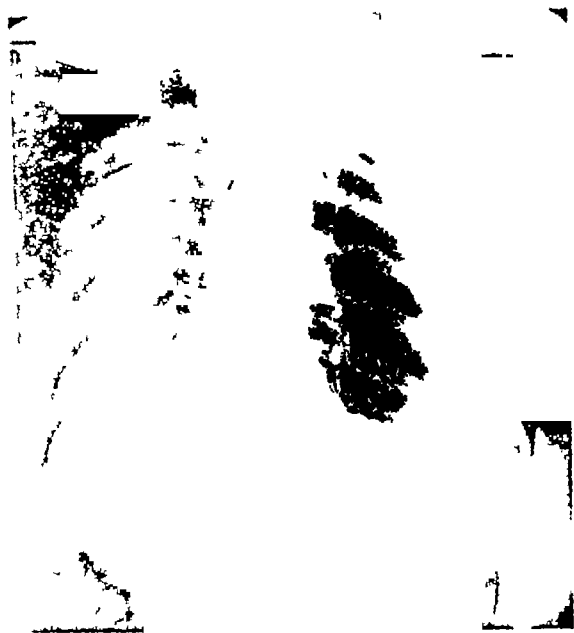


FIGURE 2 Case 5 High position of diaphragm on the right widening of the mediastinal shadow and increased density at right apex and laterally. Similar changes, when present earlier to a less marked degree had led to the erroneous diagnosis of lymphosarcoma of the mediastinum in this case of primary carcinoma of the right main bronchus. (For this and the following radiographic illustrations I am indebted to Dr Preston M. Hickey of the Department of Roentgenology, University of Michigan.)

ever, contained a rounded neoplastic mass near the apex and a massive neoplastic induration at the hilus centering about the main bronchus and forming a part of the mediastinal tumor. The great veins of the upper thorax were surrounded and compressed by neoplasm, while the right innominate vein showed a tumor thrombus. Metastases were found as listed in the summary which follows.

*Pathological Diagnosis* Primary scirrhous carcinoma of the right main bronchus with direct extension into the mediastinum and along the great vessels into the right shoulder. General carcinomatosis of bronchial nodes, lungs, thyroid and prevertebral, retroperitoneal and mesenteric lymph nodes. Hematogenous metastases into choroid plexus, spleen, liver, kidneys, adrenals, pan-

creas and prostate. Thrombosis of right innominate and subclavian veins. Edema of plexus (asphyxial death). Chronic fibroid pneumonia on the right side with bronchiectasis. Fatty infiltration of heart with serous atrophy. Atherosclerosis of aorta. Atrophy, passive congestion and parenchymatous degeneration of all organs. Chronic catarrhal gastroenteritis. Right-sided hydrocele. Old scar on left anterior thoracic wall.

*Comment* This case showed a marked degree of distention of the superficial veins providing a collateral return from the upper half of the body. Compression, of the superior vena cava and tumor thrombosis of the right innominate and subclavian veins determined the collateral circulation. It became one of the most striking features of the case. This point is discussed further in connection with Case 7. The recurrent laryngeal paralysis was also an early development and is unusual in this instance because it was bilateral. Neither bronchoscopy nor radiological visualization of the bronchial tree was attempted. Without these aids it is difficult to see how the diagnosis of lymphosarcoma could have been replaced in this instance. With them, the correct diagnosis might not have been reached for the right main bronchus, while diffusely infiltrated did not show obliteration or even stenosis.

#### CASE 6

##### WEAKNESS, ENLARGED CERVICAL NODE

*Clinical Abstract* A janitor, age 65 entered the Department of Internal Medicine complaining of a "tired feeling," weakness, a slight cough, occasional precordial pain and swelling of the extremities. He considered the onset of his illness to have occurred six months earlier when he found

that he felt tired all of the time, even after sleeping. The slight cough had recently produced a small amount of blood-streaked sputum. He had lost twenty-five pounds in weight during his illness. Examination showed a slightly tender, smooth, firm, freely movable mass, measuring 3 by 2 by 2 cms, in the right supraclavicular fossa. The patient said that this had appeared about a week before. It was removed for microscopical examination and proved to be a lymph node replaced by metastatic cystadenocarcinoma. There was a slight clubbing of the fingers. Upon X-ray examination the entire right lung field was found to show increased density with a rounded mass of greater opacity nearly filling the apex. Below this there were other areas of increased density. In the left lung field there was increased density only about the hilus. On subsequent examinations these areas of density were found to be increasing in size. A diagnosis of adenocarcinoma of the right lung with metastases was made. A series of deep X-ray treatments was given without producing favorable change in the progress of the neoplasm. Slight rise in temperature each day, gradual loss of weight and strength, periods of irrationality and general convulsions characterized the remainder of his stay in the Hospital. He died six months after admission and about one year after the supposed onset of his illness.

*Autopsy (A-1760)* Examination of the brain showed marked atrophy, congestion and edema, without evidence of neoplasm. The left lung was grossly negative in respect to neoplasm, but the right lung which showed a complete adhesive pleuritis, was filled in the upper and middle lobes with masses of new growth showing central necrosis. These were fewer and smaller in the lower lobe. The wall of the main bronchus on the right was greatly thickened and was in continuity with large tumor masses spreading radially into the substance of the lung.

*Pathological Diagnosis* Primary adenocarcinoma mucosum of right main bronchus with metastases in bronchial, cervical and

mediastinal lymph nodes and left fifth rib. Encapsulated fibrino-purulent empyema on the right side. Chronic adhesive pleuritis. Marked tumor cachexia. Atrophy, passive congestion and parenchymatous degeneration of all organs. Marked serous atrophy of all fat tissue. Marked atherosclerosis of the aorta. Secondary contracted kidney. Chronic prostatitis with cystic glandular hyperplasia. Chronic purulent posterior urethritis and cystitis. Chronic hypertrophic spondylitis with lordosis of lumbar vertebrae. Chronic focal leptomeningitis with cerebral atrophy.

*Comment* An enlarged cervical node, removed for microscopical examination proved the malignant nature of the essential pathology in this case. Clear-cut roentgenological findings, checked by negative studies of the gastrointestinal tract, served to localize correctly the process. The cerebral changes in the latter course of the disease were not due to metastases as might well have been the case but rather to the low grade renal insufficiency and to tumor cachexia.

#### CASE 7

##### PAIN IN ARMS AND CHEST HOARSENESS, PUPILARY INEQUALITY

*Clinical Abstract* A laborer, 40 years of age, complained especially of pain in the arms, commencing one and one-half years before admission to the Department of Internal Medicine. At first this pain was in the right arm and shoulder. Later it spread to the other arm, the chest and the back but never went below the waist line. With the pain there had been shortness of breath. A few months earlier for a period of about two weeks his neck, shoulders and arms had been much swollen and pitted on pressure. There had been a loss in weight of 25 pounds during two months. The patient stated that he had suddenly lost his voice in the preceding summer and it had been back ever

that time. He had noticed also that his left eyelid drooped. There had been no hemoptysis.

Examination showed the thorax to be deep and wide with expansion greater upon the left than upon the right. Over the upper sternum there was a large, rounded, hard mass, non-pulsating, slightly to the left of the midline. The veins of the anterior thoracic and abdominal wall were distended and there was a visible pulsation extending from the jugular to the superficial epigastric vessels. This was more marked upon coughing. There was no tracheal tug. The lungs showed dullness at the right apex and also at both the left apex and the left base. In addition to the drooping of the left lid with consequent narrowing of the palpebral fissure, it was found that the left pupil was smaller than the right and did not dilate well on cervical stimulation. It was believed in the Department of Neurology that these findings were indicative of a compression lesion of the left cervical sympathetic. There was also a complete paralysis of the left vocal cord. The X-ray findings were those of a non-pulsating mediastinal tumor mass, eroding the sternum, with bilateral pleural effusion. (See Figure 3.) The final diagnosis was mediastinal neoplasm, probably carcinoma of the lung.

The pleural effusion, which was blood tinged, was removed from the chest but it returned repeatedly. The mediastinal area was given roentgen irradiation both anteriorly and posteriorly. There seemed to be temporary relief from the pain but the progressive growth of the neoplasm was unchecked. The pain in the chest and arms returned with even greater severity and the patient died three months after entering the Hospital and a year and nine months after the onset of his illness.

*Autopsy* (A-2140) At autopsy a smoothly rounded, ovoid mass, 7 cms in its longitudinal diameter and 10 cms transversely, elevated 3 cms above the surrounding surface, was found to occupy the region of the upper portion of the sternum. The overlying skin was not ulcerated and the mass was firm and but slightly yielding



FIGURE 3. Case 7. Widening of mediastinum and bilateral pleural effusion, more abundant on the left, diagnosed mediastinal neoplasm. At autopsy primary medullary adenocarcinoma of upper lobe of right lung, arising in an area adjacent to the mediastinum, was found.

to pressure. Upon removing the integument, this mass was found to extend from the supra-sternal notch to the level of the third intercostal space and laterally 6.5 cms to the right of the midline and 6 cms to the left. The left pleural cavity contained 2500 cc of blood stained fluid and the right, 1500 cc. The sternum, with the neoplasm infiltrating it, was removed. Beneath the sternum the thoracic viscera. Beneath the sternum the neoplasm formed a mass about 8 cms in diameter. On the left it invaded the pericardium about the great vessels. Laterally it was firmly bound to the upper lobe of the right lung and it also extended in the left lung to its apex. The superior vena cava was penetrated and within its lumen the neoplasm extended as a completely occluding mass to, but not into, the cavity of the auricle. The neoplasm thrombus extended above into both internal jugular veins. The trachea and large bronchi were patent throughout and showed no infiltration by the new



growth The pericardial sac was heavily infiltrated and there were metastases to both visceral and parietal surfaces Pleural metastases were found over both lungs and extensions into both lungs, but the chief pulmonary mass was in the upper right lobe which was firmly united to the under surface of the sternum

Microscopic examination showed the neoplasm to be a carcinoma varying from medullary adenocarcinoma to scirrhous adenocarcinoma in type It had arisen well out in the substance of the lung, apparently in an area of chronic fibroid pneumonia

*Pathological Diagnosis* Primary medullary adenocarcinoma of upper lobe of right lung, arising in an area of old fibroid pneumonia Direct extension through pleura, tissues of chest wall, sternum and about superior vena cava and aortic arch Tumor thrombosis of superior vena cava Thrombosis of both internal jugular veins Retrograde lymphogenous metastasis downward through prevertebral chain as far as the semilunar ganglia Bilateral hemohydrothorax Atrophy, passive congestion and parenchymatous degeneration of all organs

*Comment* Throughout its course this example of primary carcinoma of the lung was characterized by pain in the shoulders, arms and chest The early perforation of the sternum was an unusual feature, for carcinoma of the lungs usually kills before there is direct extension through the thoracic wall However, Bruecken (7) described a patient upon whom a diagnosis first of gumma of the sternum and later of sarcoma of the sternum, had been made because of a similar picture Kikuth (8) found a mass the size of an apple in the left pectoralis muscles in direct continuity with a primary carcinoma of the lung The large mediastinal mass in Case 7 produced the complete group of left-

sided nerve signs, drooping of the eyelid, contraction of the pupil and recurrent laryngeal paralysis As in Case 5 the utilization of the superficial veins as a collateral venous return from the upper half of the body was an important sign A temporary engorgement of the neck shoulders and arms marked the period when this collateral circulation was becoming established Tumor thrombosis had obturated completely the superior vena cava This important sign in connection with carcinoma of the lungs and bronchi has been studied especially by Dana and McIntosh (9) who were able to show that in almost all examples of thrombosis of the superior vena cava in association with primary carcinoma of the lung the carcinoma will be found to arise in the right lung, as was true in our present case

#### CASE 8

PAIN IN THE BACK, PARALYSIS OF LOWER EXTREMITIES, "POTT'S DISEASE"

*Clinical Abstract* A female school teacher, age 40, was brought to the Orthopedic Surgery service on a Bradford frame, for pain in the back and paralysis of the lower extremities The patient had first noticed pain in her back 14 months before The pain was sharp in character and radiated toward the anterior abdominal wall She had consulted a physician for this pain for the first time seven months before X-ray examination at that time demonstrated a destructive lesion of the tenth thoracic vertebra which she was told was tuberculous A plaster jacket was applied and the patient continued teaching until the severity of the symptoms compelled her to stop She soon began to sense numbness in the feet and legs and then entered a tuberculosis sanatorium where she remained for five months Shortly after admission to this sanatorium she attempted to get

out of bed and fell. This caused severe pain in the back and within two days she had practically complete paralysis of the lower extremities with loss of control of rectal and vesical sphincters. The paralysis increased rapidly and within a week there was a complete loss of power of motion and of sensation from the umbilicus down. X-ray examination now showed destruction of the ninth, tenth and eleventh thoracic vertebrae with rarefaction of the lower vertebral bodies. There was destruction of the right tenth rib at its articulation to the spine with a loss of about two inches of its substance. A well outlined and dense shadow extended laterally on both sides of the spine from the ninth to the twelfth thoracic vertebrae. Throughout the entire lumbar spine, the sacrum and the ilium there were areas of decreased density and of increased density, such as are found in a combined osteoclastic and osteoblastic malignancy. Externally, a fluctuating swelling developed to the left of the tenth thoracic vertebra. This was incised and bloody, non-coagulating fluid escaped. A diagnosis of malignant disease of the spine was made.

In this condition the patient entered the University Hospital. The fluctuating swelling in the back having reappeared, it was incised and neoplastic tissue infiltrating the vertebral laminae found. A small portion was taken for microscopical examination. This showed a very vascular tissue infiltrated with small round cells. A tentative diagnosis of hemangiosarcoma of the spine was returned, and X-ray therapy was instituted. A week later the patient developed signs of lobular pneumonia and died two weeks after entering the University Hospital and approximately fifteen months after the supposed onset of her symptoms.

*Autopsy* (A-2284) Aside from the recent surgical incision the external examination of the body showed nothing of significance. At the mesial border of the lower lobe of the left lung a neoplastic nodule 3 cms in diameter was found. This was adherent to the vertebral column at the level of the ninth thoracic. The pre-vertebral fascia and the bodies of the

vertebrae were infiltrated with neoplasm. At the end of the autopsy the neoplasm was still considered to be of the sarcoma group, primary in the vertebrae and infiltrating the lung by extension. Microscopical examination showed that the contrary was the case. The oldest area was found to be in the mass in the lung and the greater part of the growth was a papilliferous adenocarcinoma which became scirrhous in areas. The tentative interpretation of the portion removed at operation was erroneous.

*Pathological Diagnosis* Primary bronchial papilliferous adenocarcinoma scirrhous in the lower left lobe with direct extension through the pleura into the vertebral fascia and vertebrae and with multiple hematogenous metastases in bones (vertebrae and pelvis) and liver. Generalized lymphogenous metastases in bronchial nodes and lungs. Transverse myelitis. Acute lobular pneumonia. Atrophy, chronic passive congestion and parenchymatous degeneration of all organs. Old healed glomerular-tubular nephritis. Marked lipoidosis of adrenals. Thrombosis of pampiniform plexus. Multiple pulmonary emboli. Hyaline leiomyofibroma.

*Comment* The lung shares with other organs, but particularly the prostate and the thyroid, the possibility of being the primary site of a hidden carcinoma which produces bone metastases to dominate the clinical picture. In this case the vertebral involvement was in part by direct extension and in part by metastasis. With a fairly sharply localized involvement of the vertebral column the diagnosis is apt to be Pott's disease as it was in this instance. This case is much like the thirteenth case in the series reported by Barron (10). A man, 46 years old, experienced a sudden pain in the back while playing golf and a deformity developed at once. Pain in the legs and weakness

became worse under chiropractic treatment. Pott's disease was diagnosed and he was admitted to a tuberculosis sanatorium. He had then a knuckle deformity at the twelfth thoracic. At autopsy a scirrhous carcinoma of the left lung was found.

This case was the only instance of primary carcinoma of the lung in a female in our series of twelve. Summation of statistics as given in the literature indicates a sex incidence ratio of 2.8 male to 1 female.

#### CASE 9

##### PAIN IN FEET AND LEGS, CONFUSION WITH AORTIC ANEURISM

*Clinical Abstract.* A negro laborer, age 38, entered the Bone and Joint Out-patient Department of the University Hospital on November 3rd, 1926, complaining of pain in the feet and legs. This had been present since early in September and had become progressively worse. At first it was located in the feet and ankles, but later involved the knees and was described as of sharp shooting character rather than aching. Influenced, perhaps, by a history of gonorrhea, a diagnosis of infectious arthritis with spurs was made. The patient had acquired syphilis at the same time as his gonorrheal infection. Examination at the time of entrance showed no cardiac enlargement but a loud systolic murmur and the aortic second sound was altered in character. There was a slight increase in retromanubrial dullness. There had been occasional cough and night sweats. The Wassermann was two plus. On subsequent examinations a rapid evolution of the disease process was noted. On November 22nd a slight increase in the retromanubrial dullness to the right was noted and there was a marked heaving of the precordium. There was slight dullness at the right apex both anteriorly and posteriorly. A slight tracheal tug was suspected. The liver was large and hard. A week later there was a brassy cough and slight clubbing of the fingers.

At this time the patient was discharged against advice with a diagnosis of tertiary lues, syphilis of the liver, syphilis of the aorta with aneurism, and infectious arthritis.

On December 26th the patient returned as an emergency case with all symptoms greatly increased. The liver had become enormous in size. There was now well-marked dyspnea and the cough had increased. The veins of the neck were distended. The area of retromanubrial dullness had increased greatly in size. There was limited expansion of the right chest with dullness posteriorly toward the base, decreased tactile fremitus and increased voice and breath sounds.

Röntgenological examinations showed the progress of the disease. On November 23rd a marked widening of the upper cardiac and aortic shadow to the right was reported and aneurism of the ascending aorta was suggested. On a second examination a change in the contour of the anterior borders of the lower thoracic vertebrae was shown by lateral films and there was now believed to be diffuse aneurism of the aortic arch. A month later, at the time of the second admission the entire chest picture had changed. The shadow which had been thought to be aneurism was larger and did not pulsate. The greatly increased opacity of the right hilus and greater part of the lower half of the right lung with slightly increased opacity of the hilus on the left now led to a diagnosis of secondary malignancy in the lungs. (See Figure 4.) Fluoroscopic examination following the oral administration of a barium meal showed a deformity of the lower third of the esophagus which was pushed forward by a large rounded mass in the posterior mediastinum behind the shadow of the heart. The patient died on January 11th. The final diagnosis was syphilis, aneurism of the aorta with compression of the right bronchus, syphilis of the liver, probable malignancy with metastasis to the liver, lungs and mediastinum, infectious arthritis.

*Autopsy (13-2385).* The body was that of a well developed and well nourished male negro. The abdomen was distended and more protuberant in the upper right costal



FIGURE 4 Case 9 Extensive opacity at right hilus and in lower half of right lung. Widening of upper cardiac and aortic shadow. Slightly increased opacity of hilus of left lung. At autopsy, primary carcinoma of the right main bronchus and aneurism of the lower thoracic aorta were found.

rant than elsewhere. Chylous fluid, about 400 cc in amount, was found in the peritoneal cavity. Neoplasm was not found in the left lung but on the right side the main bronchus, beginning about 2 cms below the bifurcation, was completely surrounded by neoplasm which infiltrated the wall and presented on the mucosal side as a soft, irregular elevated mass. The bronchus was much constricted at this point and also elsewhere in the secondary divisions. Surrounding the bronchi radiating extensions of the neoplasm permeated the greater part of this lung. The bronchial nodes were filled by it, the entire mass at the hilus reaching the size of a fist. In the lower portion of the thoracic aorta, just above the diaphragm, there was a large saccular aneurism, 9 cms in diameter. This was partially filled with laminated clot anteriorly but its posterior wall was torn by the eroded bodies of the ninth and tenth thoracic vertebrae. A smaller aneurismal dilatation was found separating

the muscle fibers of the diaphragm. The liver was of enormous size, measuring 32.5 by 30 by 13 cms and weighing 5030 gms. It was filled with metastases varying in size up to that of a tangerine. Gross metastases were found also in the bronchial, mediastinal, peri-pancreatic and retro-peritoneal lymph nodes and skull.

*Pathological Diagnosis* Primary medullary carcinoma of the right main bronchus infiltrating right lung. Multiple metastases in liver, bronchial, mediastinal, peripancreatic and retroperitoneal lymph nodes, and skull cap. Chylous ascites. Chronic purulent lobular pneumonia and bronchiectasis. Chronic organizing fibrinous pleuritis with right-sided pleural adhesions. Active syphilitic aortitis with aneurism of lower thoracic aorta, eroding bodies of ninth and tenth thoracic vertebrae. Syphilitic pancreatitis, adenitis and orchitis. Cardiac dilatation, more marked on right side. Fatty degenerative infiltration of heart muscle. Advanced coronary sclerosis. Marked chronic passive congestion, atrophy and parenchymatous degeneration of all organs. Marked lipoidosis of adrenals. Persistent urachus. Sub-mucosal diverticulum of bladder. Multiple adenomatous polyps of intestine. Chronic atrophic catarrhal gastro-entero-colitis. Old chronic vesiculitis and prostatitis. Old appendectomy.

*Comment* This case offered unusual difficulty in diagnosis. A negro with syphilis complained first of pain in the feet and legs. Gradually signs and symptoms of mediastinal tumor appeared. With X-ray evidence of widening of the aortic arch, aneurism was diagnosed. The liver became of enormous size very rapidly and the upper thoracic shadow radiating in outline, so that it became necessary to include malignancy in the diagnosis. At autopsy both primary carcinoma and aortic aneurism were found. In view of the erosion of the lower thoracic vertebrae by the aneurism it is

probable that the pain in the feet and legs at the onset of the disease was due to the aneurism. That this mode of onset occurs also in cases of carcinoma of the lung without complicating aneurism is shown by other cases in this series. Since the aneurism was low in the descending thoracic aorta, the brassy cough, slight clubbing of the fingers, dyspnea and distention of the veins of the neck were due to the carcinoma. The primary growth appeared within the lumen of the right main bronchus as an irregular elevated mass. If bronchoscopic examination had been considered advisable the location and character of this new growth would have rendered its diagnosis by that method an easy matter. However, with the assumption of a probable aneurism of the aortic arch, bronchoscopy was ruled out as a method of investigation.

Clubbing of the fingers as shown by this patient and also in Cases 6 and 10 occurs frequently in carcinoma of the lung. As early as 1897 Teleky (11) had included carcinoma of the lung among the many conditions which might bring about this change.

#### CASE 10

COUGH, HEMOPTYSIS, DYSPNOEA, FEVER,  
EMPYEMA

*Clinical Abstract* A mine laborer, 49 years old, had been well until eight months before coming to the hospital. From the beginning he had coughed and raised sputum which had been blood-flecked occasionally. About two months after the onset of his illness, fluid of unknown character was withdrawn from the left chest by the patient's home doctor. At that time the condition was thought to be tuberculosis and

he was moved to the county infirmary in order not to expose his family. Cough, sputum, fever, shortness of breath and weakness persisted until entrance. There had been no pain in the chest. The left supraclavicular fossa was deep and there was flattening in the left infraclavicular region. The left side of the chest was practically immobile, and much smaller than the right when viewed from behind. The percussion note was flat over the entire left chest. The fingers showed a slight clubbing. The pupils were found to be unequal, the right being smaller than the left and the pulses were not synchronous. Aneurism or mediastinal neoplasm with effusion were considered as probable diagnoses but finally discarded in favor of chronic empyema and the patient was transferred from the Department of Internal Medicine to the Department of Surgery for rib resection and drainage. This was done and a chronic empyema found. Tissue from the thickened pleura showed inflammatory changes only. X-ray examination had shown the pleura so greatly thickened on the left as to obscure the field. The fever largely disappeared for a time after drainage was instituted but bloody purulent discharge continued and the patient began to cough up blood-stained sputum. One month after the operation there was a severe hemorrhage from the chest wound. Two months later there had been no essential change. Lipiodol injection of the trachea now showed evidence of constriction of the left main bronchus. The mediastinum was found to be displaced to the left. (See Figure 5.) The constriction was verified by bronchoscopic examination but the small tissue specimen removed at that time showed granulation tissue only. A second bronchoscopic examination was made a month later and an unsuccessful attempt to dilate the bronchial stricture, which was still believed to be of inflammatory origin was made. Suction apparatus was used to evacuate the bronchial fistula, apparently with effective results. The patient now complained of a greater degree of pain in the chest. He was progressively weaker and died at the



FIGURE 5 Case 10 Marked thickening of pleura over almost entire left field Mediastinum displaced to the left Lipiodol in lower right bronchial tree (Failure of the lipiodol to enter the left main bronchus is evident in the films under strong illumination but cannot be shown clearly in reproduction because of marked density on that side)

after entering the hospital and sixteen months after the onset of his illness

*Autopsy* (A-2479) A chronic adhesive pleuritis was found on the left side, complete except for an empyema cavity containing about 200 cc of purulent fluid. Numerous bronchiectatic cavities were found throughout the left lung. These, and the bronchi themselves, were filled with mucopurulent exudate. There was diffuse atelectasis with chronic fibroid purulent pneumonia. The secondary division of the left main bronchus leading to the lower lobe was infiltrated and practically occluded by a neoplasm which infiltrated the lung extensively and metastases of which were found in the bronchial nodes and opposite lung.

*Pathological Diagnosis* Primary medullary carcinoma of left lung with metastases to bronchial nodes and right lung. Chronic pulmonary tuberculosis with cavitation.

Chronic fibroid pneumonia Anthracosis  
Chronic adhesive pleuritis Chronic empyema  
Rib resection Miliary tuberculosis of lungs, bronchial nodes and spleen  
Acute terminal purulent broncho-pneumonia  
Advanced amyloidosis of spleen (sago spleen)  
Early amyloidosis of kidneys and liver  
General marasmus Atrophy, chronic passive congestion and parenchymatous degeneration of all organs  
Aspermatogenesis  
Colloid goiter Sclerosis of aorta and pulmonary artery  
Old obliterated appendix

*Comment* Chronic pulmonary tuberculosis and chronic empyema concealed the primary carcinoma of the lung in this instance until autopsy. The empyema was undoubtedly secondary to the malignant disease, but was clinically considered the chief condition and repeated surgical operations were done for its relief. In spite of the utilization of bronchoscopy and radiological visualization of the bronchial tree the diagnosis was missed. The constriction of the left main bronchus was demonstrated by both methods but the tissue specimen removed was not taken from an area containing neoplastic infiltration. This biopsy showed chronic inflammatory changes only and was therefore in accord with the clinical conception of the case. The associated pyogenic process explained the low fever which continued throughout practically the entire course of the disease.

## CASE II

PAIN IN CHEST, PRODUCTIVE COUGH,  
WEAKNESS

*Clinical Abstract* An automobile factory mechanic, age 51, entered the Department of Surgery of the University Hospital with chief complaints of weakness on exertion, pain in the chest, loss of weight and productive cough. Sixteen months before this

he had commenced to cough and raised thick white sputum. Pain in the lower right chest began four months later. Loss of appetite and 30 pounds in weight and increasing weakness were more recent developments. Non-tuberculous pleural effusion had been diagnosed outside but three attempts to tap this fluid were unsuccessful. On examination the right pupil was found to be smaller than the left, but there was a history of an old injury to the left eye which might have accounted for the difference in size. There was limited expansion on the right side of the chest and physical signs due to either effusion or consolidation with a partly or completely closed bronchus. X-ray examination revealed an area of greatly increased density in the right lower lung field, sharply demarcated above at the level of the fourth rib anteriorly. Lipiodol was successfully introduced into the left lower and right middle lobe bronchi but none entered the bronchus to the right lower lobe (See Figure 6). The Department of Roentgenology concurred in a diagnosis of bronchogenic carcinoma made by Internal Medicine. A low fever and leucocyte count ranging from 20,000 to 44,000 were constantly present. Thoracentesis in the sixth interspace in the right mid-axillary line yielded thick pus lying beneath a greatly thickened pleura. A rib resection was then done and a distal thickened pleura and lung tissue removed from above a lung abscess which communicated with a medium sized bronchus. Following this operation the fever disappeared, the sputum decreased and the patient's general condition improved. On the fifth day after the operation he left his bed without permission and developed precordial pain, feeble pulse and dyspnoea. Two days later, about 17½ months after the reported onset, the patient died. Microscopical examination of the tissue removed at operation showed medullary carcinoma lining a part of the cavity. The final diagnosis was primary carcinoma of the right lower lobe of the lung with secondary abscess formation.

*Autopsy (A 2776)* The recent thoracotomy wound in the right axilla was filled



FIGURE 6 Case 11. Greatly increased density in lower right lung field. Lipiodol successfully introduced into the left lower and right middle lobe bronchi, but not into the bronchus of the right lower lobe. Primary squamous cell carcinoma of right main bronchus.

with a light gauze pack which was soaked with pus. Except for this area the right pleural cavity was almost entirely obliterated by adhesions. The left pleural cavity was free from adhesions and there was no fluid. The pericardium was covered with fibrinous exudate. Section of the left lung showed no neoplasm. On opening the main bronchus to the right lung it was found to be surrounded by a neoplastic mass beginning at a point 2 cms below the bifurcation of the trachea and extending particularly into the lower lobe. At a point 5 cms below the bifurcation the bronchus showed complete stenosis. The growth spread radially from this point toward the base and laterally and formed a portion of the wall of the cavity which had been opened surgically.

*Pathological Diagnosis.* Primary medullary squamous cell carcinoma of the right main bronchus with metastases in the mediastinum, lung and pericardium. Metastatic carcinoma of the liver.

tascs to right lung, bronchial and retro-peritoneal lymph nodes Chronic purulent fibroid pneumonia in lower right lung peripheral to neoplastic bronchial stenosis Atelectasis and emphysema Chronic abscess of lower right lobe (drainage of lung abscess seven days before death) Sub-acute fibrinopurulent pericarditis Right-sided chronic adhesive pleuritis Chronic atrophic catarrhal gastro-entero-colitis Chronic leptomeningitis Right-sided cardiac dilatation Acute exacerbation of chronic passive congestion and atrophy of all organs

*Comment* In view of the fact that the primary carcinoma was on the right side the smaller size of the right pupil as compared to the left was probably significant and not due to the old trauma The pain in the chest accurately indicated the primary site in this instance The secondary pyogenic infection with abscess formation, peripheral to the constricted bronchus, confused the diagnosis somewhat by giving a leucocytosis and fever Extension of the infection to the pericardial sac directly or by metastasis must have taken place before the operation for the exudate showed considerable organization This would assist in explaining the leucocytosis which reached 44,000 on one occasion

## CASE 12

### PAIN IN LOWER BACK AND LEGS

*Clinical Abstract* A sheet metal worker, 50 years old, was admitted to the Surgery Department of the University Hospital complaining of pain in both legs and lower back He believed that his trouble began with a slight injury to the foot nine months before This injury was of minor consequence but the pain in his back and legs continued, radiating from the lumbosacral region down to the posterior aspect of both legs His right leg had become functionless, apparently because of pain The

patient stated that he had lost 60 or 70 pounds since the onset of his illness There was marked tenderness of the lumbosacral region and the patient could be turned from side to side only with the greatest difficulty because of the pain occasioned by any movement of the lower back Routine physical examinations of the chest and abdomen were negative X-ray studies of lumbosacral spine and both hips showed definite changes in density which were thought to be suggestive of metastatic carcinoma The prostate was examined on several occasions and was negative except for a slight increase in size A barium enema showed good filling of the colon with no evidence of pathology A provisional diagnosis of sarcoma of the sacrum was made The patient was given several X-ray treatments over the pelvis both anteriorly and posteriorly with slight temporary relief from his pain He died four months after admission and about 13 months after the reputed onset of his disease

*Autopsy* (A-2818) Externally, the right thigh was found to be edematous and enlarged, particularly in the upper third At the root of the left lung a firm neoplastic mass, about 3 cms in diameter, was located This was in relationship to the left main bronchus and at a point 2.5 cms below the tracheal bifurcation the neoplasm appeared within the bronchial wall, infiltrating the mucosa Section of the left lung showed that the neoplasm had spread in a fan-shaped manner from the hilus, reaching practically to the apex where the largest of the masses within the substance of the lung was found The base of the heart was involved by direct extension The lower vertebrae, sacrum, pelvic bones and upper end of the right femur were filled with neoplasm metastases and were so nearly completely destroyed that they could be cut with a knife

*Pathological Diagnosis* Primary medullary small-celled carcinoma of left main bronchus Extension into pericardium Metastases in left lung, liver, pancreas, prevertebral lymph nodes, lumbar vertebrae, ilium, pubis and right femur Emphysema.



congestion and edema of lungs. Marked atrophy of heart. Subepicardial fatty infiltration. Myocardial fibrosis. Advanced coronary sclerosis. Atherosclerosis of aorta. Chronic passive congestion, atrophy and parenchymatous degeneration of all organs. Chronic pyelonephritis with old healed tubular nephritis. Chronic cystitis. Chronic catarrhal gastritis. Chronic interstitial pancreatitis. Marked lipoidosis of adrenals. Complete fibroid atrophy of testes. Thrombosis of spermatic vessels. Thrombosis of prostatic plexus extending into iliac vein and inferior vena cava. Edema of right leg and scrotum.

*Comment.* Again we have a patient whose entire clinical history is occupied by one of the distant effects of primary carcinoma of the lung—pain in the legs from metastatic involvement of the lower vertebrae, pelvic bones and adjacent soft parts. The innumerable bone metastases had produced such marked changes that primary sarcoma of the sacrum was the working diagnosis. It is unfortunate that X-ray study of the lungs was not undertaken. If this had been done a correct diagnosis should have been made for the areas of increased density would have been found to have a distribution quite unlike that of hematogenous metastases of sarcoma in the lung.

When the outstanding signs and symptoms in this series of twelve cases of primary carcinoma of the lungs and bronchi are tabulated the list closely resembles that given in the introductory paragraph. The outstanding signs and symptoms and the number of time each was encountered were as follows: Cough, 5, dyspnoea, 4, loss of weight, 4, pain in chest, 3, hemoptysis 3, pupillary changes,

3, oedema and congestion of upper half of body, 3, clubbing of fingers, 3, pain in back, 3, pain in legs 3, extension through thoracic wall, 3, recurrent laryngeal paralysis, 2, pleural effusion, 2, weakness, 2, abdominal pain 2, metastases in cervical nodes, 2, dysphagia, 2, fever, 2, cyanosis, 1, pain in arms, 1, sputum without blood, 1, vomiting, 1, pulses not synchronous at wrists, 1, drooping of eyelid, 1, coma, 1, paralysis of lower extremities, 1. The most noticeable omission from our series of cases is that of one illustrative of those which enter neuropsychiatric clinics because of changes dependent upon metastases to the brain and meninges. These form a large group in the literature but through chance assortment are not represented in our series.

The list given above does not include a new sign or symptom and it does not include one which is pathognostic of primary carcinoma of the lungs. By the very nature of the condition it becomes highly improbable that such a sign will ever be found. It is hoped, however, that by the presentation of this series of microscopically verified cases after the manner of a clinical-pathological conference—a dry clinic, if you wish—the types of cases in which carcinoma of the lung should be considered have been emphasized.

Senior medical students sometimes ask why so much effort is made to diagnose carcinoma of the lung when so little can be done about it therapeutically once the diagnosis has been established. To most of us the satisfaction experienced in arriving at a

correct solution of a puzzling clinical or pathological problem is answer enough. However, the advantages to the patient may be considerable even in the absence of therapy. Some of these cases spend much time away from friends and family and are at a considerable expenditure of money while laboring under a diagnosis of tuberculosis. Any large tuberculosis sanatorium harbors cases of primary carcinoma of the lung from time to time. Two of our series were thus treated. Others, like our Case 2, are required to submit to unnecessary laparotomy. Finally, if any progress is to be made in the surgical handling of primary carcinoma of the lungs and bronchi the medical profession must learn to recognize this condition very much earlier in the course of the disease than is done at the present time. Certain cases in which the early growth is papillomatous and endobronchial are entirely suitable for removal through the bronchoscope (3), while in other cases early carcinoma well out in the parenchyma may be removed by partial lobectomy. Brunn (12) found that there are reports of at least 28 instances of surgical intervention for this condition in the literature. Perhaps the stage at which carcinoma of the lung is diagnosed has already been moved back from the autopsy room to the last few months of life. It must be set back by a very much greater interval if there is to be any chance for successful intervention.

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# The Blood as a Diagnostic Aid in the Differential Diagnosis of the Lymphadenopathies\*

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IN any discussion of the blood as a diagnostic aid must come a reiteration of the now generally accepted belief that changes in the blood do not constitute a disease but are merely manifestations of what is taking place in the blood forming organs. Vogel (1) has called attention to this in an excellent analogy between the blood as a secretion, and the gastric juice. The absurdity of calling hyperchlorhydria a disease of the gastric juice makes any consideration of "diseases of the blood," as such, untenable. Piney (2) says

"To-day we have had to give up the older conception of the blood as a special form of connective tissue with a fluid matrix, we have to regard it as a composite containing the products of all the hematopoietic tissues."

We pass on then to a consideration of the lymphadenopathies with a better idea, perhaps, of what not to expect in the way of constancy of changes in the blood in these complex conditions. Moreover in the absence of any histological differentiation in lymphosarcoma leukemia and pseudo-leukemia one wonders (and that in conjunction with many others) whether these are not all the same

disease in various expressions or exhibitions of reaction to the same underlying cause. Typhoid fever for example may express itself in many ways occasionally with mental symptoms predominating, sometimes respiratory, sometimes abdominal, at other times renal. Why is it not logical to expect, particularly in view of the similar histology that lymphosarcoma leukemia and pseudo-leukemia are analogous expressions of some disease process, with the blood picture only one symptom of the clinical syndrome? The leukosarcomata may furnish the clue to bridge the gap exhibiting a lymphosarcomatous type of tumor pathologically terminating with the picture of an acute leukemia.

In differentiating the group of lymphadenopathies we fall back at once to weed out one member on a purely pathological basis. Biopsy at present enables a definite diagnosis in the great majority of cases in Hodgkin's disease only. The very early stage of lymphoid hyperplasia is of course not pathognomonic but the later

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picture of proliferation of the reticulo-endothelial cells, giant cells and eosinophiles, stamps this disease in unmistakable fashion. Histologically, lymphosarcoma, leukemia and pseudo-leukemia have nothing to differentiate them. The term "pseudo-leukemia" requires definition, as this nomenclature has been used at different times to designate more than one condition. We shall defer this definition, however, until pseudo-leukemia itself is taken up later in the course of this paper.

Clinically, the differential diagnosis of enlargement of the lymph nodes is not readily made. In recent years further to complicate the clinical picture, have come the recognition and renewed studies of infectious mononucleosis (glandular fever, acute benign lymphoblastosis). Its very close resemblance to the leukemias has given rise to grave doubts in the diagnosis in many instances. The literature abounds in reports of cases which, because of blood cell changes and clinical findings, have been thought to be leukemia.

It is our purpose to point out the diagnostic aids to be derived from a study of the blood in the lymphadenopathies. We shall begin with the closest simulator of leukemia, namely infectious mononucleosis.

#### INFECTIOUS MONONUCLEOSIS (GLANDULAR FEVER)

Observers (3, 4, 5) are agreed that there is almost always a lymphocytosis and moderate increase in the total number of white blood cells, together with a blood picture which might be confused with acute leu-

kemia. Longcope (6) remarks the very striking resemblance to leukemia, but hastens to point out that the clinical picture,

"early and marked enlargement of the lymph nodes, the absence of anemia and of purpura," and "the histological and biological character of the abnormal mononuclear elements or the blood, practically exclude the possibility of considering these cases as instances of mild and transient leukemia."

The classification of the type or types of cell met with is difficult. Downey and McKinlay (7) have described three separate types. They add

"nearly all of the lymphoid cells of the blood, when first examined, were atypical to the extent illustrated in the figures. The size and form of the nucleus are of little value in determining genetic relationships or stages of differentiation of the cells, but the quantity and distribution of chromatin and its relation to the parachromatin is of great importance."

Baldrige (8) and his co-workers report variation in the blood findings. Leucocytosis of varying degree was present sometime during the course, in most cases. In most instances, cases with marked temperature reactions showed a leucocytosis with relative polymorphonuclear increase during the course, particularly while temperature persisted. The largest total leucocyte count was 26,950. "Most of the cases which were followed developed a leukopenia at some time during their course, usually in from two to four weeks after the onset." The lowest count was 3,400.

The average of 136 counts on 50 patients, as given by them, are as follows

WBC	Polys	Monos	Eos	Baso	RBC	HGB
10,177	48.4	50.2	1.1	0.2	2,800,000	92.2

Their summary of noteworthy blood findings is

- 1 Leukocytosis sometime during the course of the disease, usually at the onset and as a rule not above 20,000
- 2 During convalescence total white count below average normal frequently met with
- 3 Percentage of mononuclears appears to average higher in sporadic than in epidemic cases
- 4 Degree of fever and polynuclear increase appear related
- 5 Mononucleosis develops as the fever subsides

Cotrell (9) recently studied 12 cases of infectious mononucleosis and observed

- 1 "An increase in the lymphocytes amounting to 40 per cent or more of the total leukocytosis"
- 2 "Increase in the total number of leukocytosis"

#### CHARACTER OF THE MONONUCLEAR CELLS

The mononuclears, although abnormal, differ from the cells seen in lymphatic leukemia. Bloedorn and Haughton (5) point out that these cells do not show the "poor staining reaction of the cytoplasm and nucleus" seen in leukemia. Furthermore, no degenerated cells were seen in their series of acute benign lymphoblastosis cases, such as are frequently met with in the acute leukemias. They add

"The heavy staining nuclei of the lymphoblast in this disease may be placed centrally or eccentrically. It is often round, oval or irregular in outline show-

ing deep indentations and occasionally showing the clover leaf or bilobed Rieder type nucleus. Occasionally, azure granules were noted in the cytoplasm and vacuoles in the dark opaque blue were not infrequently noted. None of these cells showed an oxidase ferment, thus differing from those of myelocytic origin.

"The small lymphocyte, as a rule, stained normally with Wright's stain, but the majority of cells making up this group consist of large lymphadenoid cells with a protoplasm so darkly stained that it is at first difficult to distinguish them from myelocytes."

Weil (10) has called these cells "non-granular myelocytes" and described them as follows

"They look like a myelocyte whose granules have fused into a smooth homogeneous band of color around the spherical or ovoid nucleus. The protoplasm is homogeneous and deeply stained."

Moise (11) notes that the blood smear is different from that in leukemia. There is an absence of "immature, atypical and degenerating forms of leukocytes and the presence of large numbers of the bilobed or Rieder type of white cell is quite distinctive."

Baldrige (8) and his co-workers have described the abnormal cells as follows

"The size varies from but little larger than the small lymphocyte to cells as large or even larger than the largest cells of normal blood. The inner structure of the nucleus in some is like that of the normal lymphocyte in that it is made up of irregular bands of chromatin which give it a rather wavy appearance.

Nucleoli are not at all common. Occasionally nuclei are met with in which there is a very marked condensation of chromatin near the periphery giving a suggestion of the clock-face pattern.

seen in plasma cells. The chromatin arrangement within the nuclei of many of the cells in our series was very close to that seen in normal monocytes.

"The cytoplasm of the cells varies somewhat in amount but is usually more abundant than in the normal lymphocyte. Stained with modifications of the Romanowski method there is a great variation in the number and size of azurophil granules."

Downey and McKinlay (7) warn that the "finding of an occasional immature cell does not warrant the diagnosis of acute leukemia even though the clinical picture is suggestive."

Sprunt and Evans (3) discuss the difficulty in differential diagnosis from a beginning lymphatic leukemia. The more marked anemia, tendency to hemorrhage and fragility of the cells with the production of "smudges" in the blood smear, point to an acute leukemia. The blood picture in infectious mononucleosis, according to them, shows usually a normal or only slightly increased leukocyte count in the first few days, followed by a leukocytosis of 13,000 to 20,000 per cmm, with an increase in percentage of mononuclears.

others (Sprunt and Evans (3) and Schenck and Perry Pepper (12)) are not so optimistic. The latter authors write

"Some believe that the differential diagnosis can be made from a careful study of the predominating type of cell but this is very difficult."

Baldrige and his co-workers (8) believe that

"While certain individual blood cells may be found in glandular fever which resemble the very unripe elements of acute leukemia—in our experience a differential study of 100 cells has been ample to establish the diagnosis."

Bloedorn and Haughton (5) remark

"Nevertheless the resemblance to leukemia has been so striking in some of the cases that eminent hematologists have considered it impossible to differentiate this condition on the blood smears alone."

Schenck and Perry Pepper (12) also serve

"It is quite possible to believe that certainly on the blood picture alone, it will be impossible to differentiate between certain cases of infectious mononucleosis and acute leukemia."

some are anxious to lead along paths that most others are not ready to follow, is it not wisest for us to pause and look longer before we go on?

### HODGKIN'S DISEASE

From the many studies on the blood made in this condition, the conclusion is warranted that there is little specific in the blood picture. A secondary anemia is commonly present, although the red blood cells are not usually greatly reduced. Naegeli (13) notes the hemoglobin seldom under 60-80 per cent. In a few cases, severe anemia has been noted. Frankel and Much (14)—1,140,000, Hirschfeldt (15) 1,000,000 with hemoglobin of 20 per cent. On the other hand, where much cyanosis and dyspnoea are present as a result of compression, high red counts and hemoglobin have been reported (Naegeli (13)) up to 6,000,000 and HB 125.

Sir Humphrey Rolleston (16) observes

"The white count does not show any constant or characteristic change. Usually leukocytosis is absent and there may be a leukopenia with a relative lymphocyte increase, especially, I believe, when the spleen is predominantly affected, a view shared by Weber (17)."

Naegeli (13) notes leukopenia particularly in the abdominal forms of the disease.

Various observers have called attention to certain phases they deemed characteristic, but these findings have, on the whole, not been demonstrated consistently enough to warrant their designation as typical of this disease. Bunting (18) believed that the most striking feature of the white blood

cell count was a high percentage of transitional leukocytes in all stages, due possibly he suggested, to the proliferation of the endothelial cells of the lymph nodes. Though he believed the findings to be of diagnostic value, others (Perry Pepper (45)) have questioned their importance.

The latter author says

"A relative or even an actual increase in the mononuclear and transitional cells seems to be the most constant finding but this is far from being pathognomonic of Hodgkin's disease."

Steiger (26) thinks that the differential leukocyte count is characteristic of the stage of the disease, namely a lymphocytosis in the early stage of lymphoid hyperplasia, a neutrophilia in the second stage, and, finally, a lymphopenia in the last stage with onset of fibrosis. It is very doubtful, however, that such a rigid grouping can be made. It is pointed out that it is usual for the disease to be present in different stages in different lymph nodes and therefore unlikely that a clear cut blood picture should be present at any time assuming the basis of the differentiation to be true.

In a later study, Bunting (46) noted the absence of a single constant blood picture in Hodgkin's. He believes, however, that two groups of cases can be distinguished

1. Those of a duration of one year or less
  - A Normal or somewhat increased leukocyte count and a normal or slightly decreased percentage of polymorphonuclears
2. Cases of more than one year's duration
  - A Sharp leukocytosis
  - B High percentage of polymorphonuclears

and throughout the disease

- 1 An increase of transitional leukocytes
  - 2 A gradual decrease in the lymphocytes
- Piney (2) (page 142) remarks that "leukocytosis is almost invariable and there is no other disease (in which clinical evidence of infection is absent) in which a very high number of leukocytes can persist for so long a time"

Naegeli (13) makes a similar observation as to the persistent leukocytosis, reporting six cases from personal observation, with counts of 41,000, 45,000, 46,000, 48,000, 50,000 and 55,400

*Comment* In brief, then, although many conditions of interest in the blood picture have been observed in Hodgkin's disease from time to time, looking at the broad vista of accumulated evidence we are led to agree with Piney's (2) remark that "the blood changes in Hodgkin's disease are far from spectacular"

#### PSEUDO-LEUKEMIA

Much difference of opinion exists as to the correctness or advisability of retaining this nomenclature which was first used by Cohnheim (27) in describing a condition presenting anatomical characteristics similar to the leukemias previously described by Virchow (28), but having no changes in the blood. Naegeli (13) uses the term to denote a "symptom-complex" and not a disease, denoting, by pseudo-leukemia, conditions resembling the external appearance of leukemia (enlargement of the lymph nodes and spleen), but lacking the blood changes of leukemia

Jagic (29) says

"From a clinical standpoint we can dispense with the term 'pseudo-leukemia' because in the majority of instances we are able to make a clinical diagnosis which corresponds to the recognized anatomical picture"

As used here, the term "pseudo-leukemia" is not related to aleukemic leukemia. By the latter term we mean to denote that stage of a true leukemia in which the blood picture does not show the high leucocyte count typical of the disease, although the differential count is almost always suggestive

In using the term "pseudo-leukemia" we refer particularly to that condition which some observers believe is an entity, both from the clinical and anatomical standpoint. We have no reference here to the so-called aleukemic phase of leukemia. Symmers (47), for example, out of a large experience with diseases of the lymphoid apparatus, points out its anatomical and clinical characteristics, particularly with reference to its clinical resemblance to leukemia, Hodgkin's disease, lymphosarcoma, and the like, and its gastro-intestinal manifestations, which are sometimes extraordinarily extensive. This observer's definition of the disease concurs with that of Cohnheim (27), they agree that it is a disease with all the anatomical characteristics of chronic lymphatic leukemia, without changes in the blood

Pseudo-leukemia presents no blood changes to differentiate it from lymphosarcoma, nor is there any histologic difference demonstrable in the lymph nodes or elsewhere. Pseudo-leukemia, according to Symmers (30),



'produces no destructive infiltration of tissues but limits its activities to the lymphoid structures, and the spleen is almost invariably enlarged, whereas the opposite is not unusual in lymphosarcoma'

The blood count given in one of Symmers' (48) cases of pseudo-leukemia was

WBC	Polys	Small Lymphs	Large Lymphs	Eos	Baso	RBC	HB
11,000	72	24	3	1		5,240,000	80

In cases previously reported in the literature, there is no outstanding feature in the blood examination, only slight leukocytosis being reported—11,800 by Carrington (31) and 10,600 by Celler (32)

#### LEUKOSARCOMA

Sternberg (33) used the term leukosarcoma to denote a group of cases characterized by a leukemic blood picture and an invasive lymphoid tumor. That this condition is an entity unrelated to leukemia is not believed by most observers. Turk (34) and

Naegeli (13) consider leukosarcoma as only a stage of lymphatic leukemia.

When the case is fully established, the leukemic blood picture present resembles, in most respects, that found in acute leukemia. There is a high percentage of large lymphoid or so-called "leukosarcoma" cells. Small lymphocytes are not predominant.

Early in the disease the leukemic blood picture may not be manifest, the symptoms at such time being referable solely to the presence of the invasive tumor, most often of mediastinal origin.

In connection with this location of the tumor growth, it is of interest to note, as Symmers (30) points out, "the astounding, if ominous fact that in these circumstances the changes enumerated may stretch themselves over an extended period without eliciting any complaint from the patient and both subjective and objective disturbances may be registered suddenly and without warning at a time when anatomic expansion has advanced beyond all hope of control."

Webster (35) gives the following counts in cases of leukosarcoma, in various phases:

	W B C	Polys	Small Monos	Eosin	Trans	R B C	H B
Case 1	33,000 4,000	21.8 74	76.0 21	0.8 2.8	0.0 0.4	5,200,000 4,588,000	
Case 2	230,500	(Differential not given)				Small lymphocytes pred.	
Case 3	3960 87,400	00 0	32 43	Smudges 57%			

Sternberg's (35) case, about ten days before death, showed

W B C	Polys	Lymphs	Large Monos	Myelocytes
6,800	5	6	85	4

#### LYMPHOSARCOMA

When Kundrat (36) first described the condition now known as lymphosarcoma, namely a diffuse proliferation in lymphoid structures of lymphocytes in an inconspicuous stroma, he propounded as a characteristic of the growth its tendency to remain confined within sharp limits. He noted, however, its capacity to invade locally and often extensively. Symmers (30) very recently has reported a study of 17 cases, 9 of which, as the author states, "fulfill faithfully Kundrat's maxim of local growth", the other 8 "have brought about a degree of territorial expansion seldom distanced by any of the other diseases of the lymphoid apparatus". It is important to note this writer's observation of the many clinical similarities between Hodgkin's disease and lymphosarcoma and even in the early stages, of the histological resemblances, when the picture in both shows a simple, diffuse hyperplasia of the lymphoid cells. In none of his cases was there anything typical in the blood picture, the two cases terminating with a blood picture of acute leukemia coming under the classification of what has been described as leukosarcomatosis.

There is nothing characteristic in the blood picture of any type of lymphosarcoma; anemia is often absent. Negele (13) notes a reduction of the

lymphocytes, recording the following counts

W B C	Lymphs
6,000	33%
5,000	18
7,000	15
10,400	7
8,600	15
7,200	27 large lymphs
21,600	2
6,800	19
4,600	16
11,460	6
41,500	6 (case had metastasis to skin and bone marrow)

Pathologic forms of lymphocytes have not been observed in lymphosarcoma, occasionally large lymphocytes were noticed but no lymphoblasts.

This author notes that the diagnosis of the condition in progressive cases is usually not difficult, particularly in the mediastinal ones, being, as they are, made on general clinical observation and not on blood findings. There may be a moderate leucocytosis, but there is nothing unusual in the differential count.

#### LEUKEMIA

To discuss the blood findings and variations possible in the different types of leukemia, acute and chronic with their subdivisions, is far beyond the province of this paper. Some pertinent facts, however, must be alluded to. The temporary resemblance to leukemia of the blood picture in some cases of infectious mononucleosis has already been pointed out. The suggestive relationship of leukosarcoma and lymphosarcoma to the leukemia has been referred to.

Some general remarks on the blood picture in leukemia are of interest. Dittus

lielmo (37) notes that the 'more acute the leukemic process the less mature and differentiated appear the cellular forms which are carried from the place of their original location into the blood stream"

In the most acute form of leukemia he observed the predominance of hemocytoblasts, in the less rapid type, the more differentiated elements appear (myeloblasts in the myeloid type, lymphoblasts in the lymphatic type) and in chronic cases the number of granular cells, lymphocytes and monocytes are greatly increased

What interests us particularly are those types of leukemia frequently referred to as aleukemic leukemia By this term we mean to denote, as previously pointed out, those cases proved at some time to be true leukemia, but which, at the particular time the case comes under observation, show a normal or decreased total white count This type of case offers a difficult problem, at times, in differential diagnosis

Naish and Tingle (38) reported a case of leukemia with a complete absence of any, even temporary, leukocytosis, showing a low total number of polymorphonuclears with a stability of the leukocyte count over a long period The count, on one occasion

Autopsy showed leukemic infiltration of the liver and spleen

Fox and Farley (39) report two cases of aleukemic leukemia, one of which was an undoubted case and proven at autopsy, the other case did not come to autopsy but the biopsy excluded Hodgkin's disease

They note

"The two cases of aleukemic leukemia reported, while showing extensive involvement of the lymphatic apparatus, gave no reduction of circulatory mononuclears, a relative reduction being a picture usually seen in granulomata and sarcomata, involving much of the lymphatic apparatus This point should be a decided help in clinical differential diagnosis"

Jaffee (40) finds that 'normal or subnormal leukocyte counts in typical myelogenous leukemia are far from rare" He reports two cases of aleukemic myelosis (the aleukemic form of myelogenous leukemia) in which 'the excessive proliferation of the myeloid tissue—caused no characteristic change of the blood picture and the true nature of the disease was revealed only by the histologic study of the organs involved" In true aleukemic myelosis, he adds, the white blood picture remains normal, giving no information as to the extensive proliferation of the myeloid tissue

Brill (41) discussing aleukemic leukemia notes that 'a careful examination of the blood however usually shows abnormal white cells par-

W B C	Polys	Small Monos	Large Monos	R B C
2,900	25	13	62	850 000

	W B C	Polys	Lymph	Mono	Trans	Eos	Baso	R B C	Hb
Case 1	5,000	54	38	0	1	4		4 670 000	85
(Autopsy)	6,500	52	40	3	3	1	1	5 400 000	93
Case 2	13 800	43	30	11	7	3		4 800 000	82
	28 000	77	16	0	1			4 810 000	

ticularly characterized by qualitative changes

*Comment* Doubtless, much more might be said about rare types of leukemias. It is sufficient for our purpose, however, to call attention to some of these problems as relating to the leukemias and to point out that at times confirmation of the diagnosis leukemia may be lacking in the examination of the blood.

#### FOLLICULAR LYMPHADENOPATHY WITH SPLENOMEGALY

Very recently there has been described (42, 49) a condition, perhaps first noted by Becker (43), of generalized enlargement of the lymph nodes with splenomegaly. The nodes involved may be superficial or deep or both. Histologically, as Symmers (49) observes, the picture is characterized "almost exclusively by numerical and dimensional hyperplasia of the germinal follicles." Clinically, it presents essentially gross identical features with Hodgkin's granuloma, chronic lymphatic leukemia, pseudo-leukemia and lymphosarcoma, except that, even if untreated, it does not menace life.

Thus far, if Becker's (43) case be included, only six cases have been reported. The lesion appears to be definitely and favorably affected by the X-ray.

There is nothing characteristic in the blood, biopsy, only, enabling the establishment of the diagnosis.

The fact that this condition is benign sheds the first ray of hope on this group of lymphadenopathies which, aside from infectious mononu-

cleosis, have led to a uniformly fatal termination.

#### TUBERCULOUS LYMPHADENITIS

Although the process is most often localized, there are some cases in which widespread involvement occurs, closely resembling the external anatomical characteristics of Hodgkin's disease and the leukemias. Biopsy, of course, at once makes the diagnosis clear, but from the standpoint of the blood alone there is nothing specific in the hematologic picture.

Nægelı (13) notes a marked reduction in the leukocytes in most cases, calling attention, however, to the occurrence of a moderate leukocytosis in some instances. In connection with the low white count usually present in tuberculosis, he warns of that phase of leukemia in which the white count is relatively normal or even lower. In one of his cases of generalized lymph node tuberculosis, shown in all the nodes histologically at autopsy, there was a leukopenia of 2-3-4,000 (numerous counts in two years) with a reduction of the lymphocytes (300-500 per cmm).

Bäumler (50) reported similar low counts in his case, and Fabian (quoted by Nægelı (13)) reported a case with a count of 3,800 white blood cells, with 92 per cent polymorphonuclears and only 5 per cent lymphocytes.

Severe anemia, according to Fleischmann (51), seldom occurs in generalized tuberculous granuloma, but Nægelı (13) was able to demonstrate polychromatophilia and basophilic stippling even when anemia was absent.

In a general way, according to the latter author, from the standpoint of

differential diagnosis a leukopenia is against Hodgkin's disease and for tuberculosis, whereas a distinct leukocytosis is strongly in favor of Hodgkin's and has as yet never been found in diffuse tuberculous lymph granuloma

### SUMMARY

The writers have attempted, by a study of the pertinent literature, to point out the diagnostic aids to be derived from examination of the blood in Hodgkin's disease, lymphosarcoma, leukosarcoma, pseudo-leukemia, leukemia, follicular lymphadenopathy with splenomegaly and tuberculous lymphadenitis. They wish to acknowledge that in many cases they have drawn freely from the writing of those quoted.

On the whole, up to the present time, there is no specific blood picture in Hodgkin's disease, in the so-

called pseudo-leukemia or Cohnheim, in lymphosarcoma, leukosarcoma, in the benign follicular lymphadenopathy with splenomegaly or in tuberculous lymphadenitis. Some characteristics (increase in transitional leukocytes, particularly) have been pointed out for Hodgkin's disease, but their value is questionable from a diagnostic standpoint. The chief difficulty, at present, lies in the differential diagnosis between infectious mononucleosis and the aleukemic stage of lymphatic leukemia. Difference of opinion as to the solution of this problem on the blood findings alone still exists among competent observers.

If we have shed no new light on the problems of the lymphadenopathies, we trust that we have illuminated those already explored realms now resting, perhaps, too comfortably in the shadow of the great heap of accumulated data.

TABLE I—BLOOD COUNTS IN INFECTIOUS MONONUCLEOSIS  
(Downey & McKinlay (7))

Case	Date	W B C	Polys	Lymph	Lymphs		Tr	L M	R b C	HB
					Sm	Lgc				
1	3/ 6/21	3,000								
	3/12/21	17,200	20	80					3,000,000	
	11/ 3/21	7,000	56		8	37	1			
	2/24/22	7,150	55		21	17	4	3		
	6/ 8/22		71		29					
2	11/ 3/21	16,100	21		8	67	4		6,000 (600)	55%
3	3/ 8/22	26,200	25	74				1	5,184,000	60
	6/ 1/22	7,000	38	57				5	4,002,000	55
4	4/10/22	26,000	18	77			1	1	4,410,000	75
	6/ 5/22	8,400	46	45			4	5	4,410,000	70
5	5/ 9/22	11,600	32	56			6	6	4,200,000	50
6	12/15/21	10,700	41		40	15	1	1		70
7	8/15/22	12,800	13	77			1	0		70
8	9/26/22	15,000	43	57						80
9	10/30/22	11,750	50		23	13	5	3		
	11/ 7/22	5,850	42		46	0	4			

TABLE II—BLOOD COUNTS IN INFECTIOUS MONONUCLEOSIS  
(Chilbert, W. C. and Harrison, J. F. 1931)

Case	Date	W B C	Poly	Lym	Mono	Tr	M.C.			RBC	Hb
							Leu	Cell	M, el		
1	1/18/20	10,000	1	54						4,200,000	75%
	12/ 2/20	10,000	2	52	0.5	1	20	1		5,400,000	100
2	10/18/20	9,100	2.1	74	1	2				4,700,000	90
	12/ 1/20	7,000	2.1	25	2	0.5	0.5			5,200,000	100
3	11/ 2/20	20,100	2.5	24	1			1			
	12/ 2/20	7,000	1.5	54.5	2	1	3	0.5		4,000,000	95
4	12/ 6/20	6,000	10	51		2		0.5			
	12/ 6/20	7,200	5.3	39		1.8	1.5	2		5,500,000	100

TABLE III—BLOOD COUNTS IN INFECTIOUS MONONUCLEOSIS (GRANULAR FEVER)  
(Baldridge, et al. (31))

Case	Date	W B C	Polys.	Monos	Leu	Bas.
1	5/27/18	11,200	15	85		
	6/11/18	3,000	30	64		
	6/25/18	5,800	60	38		2
2	6/31/18	13,400	11	59		
	1/29/24	15,150	60	31		
	6/ 4/24	8,500	13	57		
3	3/ 5/25	8,000	52	48		
	12/31/24	17,000	70	30		
	1/16/25	8,400	51	45	2	2
4	1/26/25	7,700	37	60	3	
	10/23/25	7,550	41	50	3	
	11/28/22	21,250	9	90	1	
5	12/ 1/22	25,200	13	86	1	
	12/ 6/22	10,500	56	44		
	12/ 8/22	8,250	41	59		
6	12/14/22	6,500	32	63	5	
	1/ 6/25	7,200	59	40	1	

## SUMMARY—INFECTIOUS MONONUCLEOSIS

	Cases	Counts	Total	W B C	Poly	Lymph	Tran	L M	Eos
Table 1	9	15	185,750	12,385	38.4	56.5	2.4	2.6	1.0
2	4	8	93,500	11,690	41.2	54.6	1.2	1.0	1.0
3	4	17	188,200	11,070	42.6	56.2			
	17	40	467,450	11,685	40.7	55.8	1.2	1.2	0.7

The very close similarity in the total white and differential count by three independent groups of observers is striking. The character of the mononuclears is the outstanding factor in differential diagnosis and unfortunately this cannot be manifest in any tables such as these.

TABLE IV—BLOOD COUNTS IN HODGKIN'S DISEASE  
(McAlpin, K. R. (19))

*Untreated Cases*

Time Since Onset	Case	W B C	Platelets	Neutro	Lym	Eos	Tr	Bas	Myel	Leuko-cytes
3 Months	1	13,000	680,000	89.6	4.6	3.0	2.2			0.6
3½ Years	2	11,000	400,000	47.8	34.8	7.8	7.0	0.4	0.4	1.8
1½ Years	3	10,900	36,000	86.2	9.4		3.6	0.2		0.6
3 Months	4	10,000	150,000	78.4	18.3	0.3	3.0			
6 Weeks	5	8,800	230,000	62.0	22.0	12.0	3.7	0.3		
4 Years	6	7,200	210,000	69.0	26.4	0.6	3.7	0.3		
1 Year	7	6,000	200,000	61.4	32.4	1.3	4.6	0.3		
1½ Years	8	4,900	150,000	67.4	26.0	2.6	3.2	0.8		
8 Months	9	4,200	150,000	54.4	31.3	5.0	3.0	0.3		
2 Months	10	4,000	180,000	71.6	20.6		7.4		0.2	0.2

*Treated Cases*

5½ Years	1	10,000	340,000	79.6	3.0	0.2	17.0	0.2		
5 Months	2	8,200	350,000	71.8	17.6	2.4	7.6	0.6		
2 Years	3	7,000	370,000	76.4	13.4	4.8	5.0	0.2		0.2
19 Months	4	6,000	550,000	78.6	6.8	3.2	11.2	0.2		
16 Months	5	5,700	300,000	78.0	11.2	2.2	6.6			2.0
3 Months	6	4,500	280,000	65.8	31.0		2.8			0.4
15 Months	7	4,300	470,000	70.8	20.0	3.8	3.6	1.2	0.6	
4 Months	8	2,000	45,000	32.5	62.0		5.0			0.5

TABLE V—BLOOD COUNTS IN HODGKIN'S DISEASE  
(Cunningham, W. F. (53))

Case	W B C	Polys	Lymphs	L Monos	Tr	Eos	Baso	R.B.C	Hb
1	74,000	91.7	3.3	2.3	2.4		0.3	4,150,000	70
2	15,000	76.8	6.7	0.8	12.6	2.3	0.5	4,300,000	60
3	20,000	80	11.0	1.8	0.0	0.5	1.15	5,600,000	75
4	14,000	69	20	2.3	7.3	1	0.3	3,500,000	50
5	12,000	68	22.3	2.3	5.0	2.3		4,300,000	60
6	11,000	78	11.5	3.3	5.8	0.0		3,750,000	50
7	19,000	72.5	19.0	0.6	5.3	1.3		5,550,000	70
8	16,000	73.5	17	0.5	7.0	0.0		4,800,000	64
9	62,000	92.0	1.5	2.3	3.5	1.3	0.15	4,700,000	54
10	12,000	71.0	15	5.3	0.3	1.5	0.0	4,000,000	60

TABLE VI—BLOOD COUNTS IN HODGKIN'S DISEASE  
(Lemon, W B and Doyle, J B (52))

Case No	W B C	Polys.	Lymphs	Large Monos	Eos	Baso	R.B C	HB
1	23,900	48 0	23 3	4 3	27 7	0 7	4,400,000	80%
2	12,800	81 7	9 3	2 7	1 0	0 3	3,770,000	50
3	5,200							65
4	5,200						4,720,000	85
5	3,000	59 7	30 7	9 0	0 0	0 7	3,250,000	57
6	7,000	86 7	5 7	6 7	0 7	0 3	3,720,000	61
7	13,200	78 7	12 7	5 0	3 7	0 0	4,880,000	88
8	8,600	81 0	10 0	6 3	2 0	0 7	5,240,000	70
9	8,200	50 0	36 3	10 0	2 7	1 0	4,040,000	68
10	23,000	85 0	8 7	3 0	3 3	0 0	4,510,000	64
11	10,000	65 7	18 0	15 3	0 0	1 0	4,060,000	64
12	12,200	85 0	6 7	6 3	2 0	0 0	4,400,000	70
13	8,600	86 3	5 0	4 7	3 3	0 7	3,760,000	55
14	16,400	89 0	6 5	4 5	0 0	0 0	3,260,000	47
15	19,500	83 5	9 5	5 5	1 5	0 0	4,880,000	70
16	13,800	82 0	12 0	4 0	2 0	0 0	4,720,000	74
17	7,800						3,760,000	55
18	8,400						4,400,000	58
19	4,900	90 0	5 0	5 0	0 0	0 0	4,400,000	53
20	8,600						3,460,000	45
21	17,400	84 0	11 5	3 5	1 0	0 0	4,260,000	68
22	10,200	76 0	19 5	3 5	1 0	0 0	4,800,000	62
23	15,400	87 5	7 5	5 0	0 5	0 0	4,240,000	50
Average	13,370	77 7	13 2	6 1	2 9	0 3	4,230,000	67

for 18  
cases  
1 5  
for 17 cases

TABLE VII—BLOOD COUNTS IN HODGKIN'S DISEASE  
(Symmers, D (54))

Case No	W B C	Polys	Lymphs	Large Monos	Tr	Eos	R B C	HB
1	7,000	76	20	2	2		2,300,000	35%
2	18,000	94 5	2 5	1 5	1 5			
3	2,200	85	10	2	3		3,800,000	
4	13,200	92	5	2	1			
5	6,700	69	24					
6						7	2,568,000	60
7	5,200	64	21	6	9		2,910,000	
8	14,800	59	39		2		2,400,000	18
9								
10	16,200	92	7				3,800,000	70
11	17,500	80	9	3	2	1	4,200,000	65
12		78	17	(5 mast cells)			4,400,000	
13	6,600	66	20	10	4		4,912,000	
14	11,000	80					2,400,000	



## SUMMARY OF HODGKIN'S DISEASE

	Cases	Counts	W B C	Poly	Lymph	Eos	Tr	Bas	Mye	Plate-lets
Table 7	14	11	10,765	80.9	14.6	0.7	2.0		2.2	
Table 4										
Untreated	10	10	8,000	68.8	22.6	3.3	4.1	0.3		238,600
Treated	8	8	5,960	69.2	20.6	2.1	7.3	0.3		338,125
Table 5	10	10	25,500	77.2	12.8	1.1	6.1	0.3	2.2	
Table 6	23	23	13,370	77.7	13.2	1.5		0.3	6.1	
Average	65	63	12,720	74.8	16.8	1.7	3.9	0.24	2.1	

This summary is self explanatory. Relatively wide variation in the total white count is noted and though the differential count tends to greater similarity, there is nothing characteristic.

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# Roentgenography in its Relationship to Clinical Findings in Pulmonary Tuberculosis\*

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A GREAT deal of confusion exists in the interpretation of roentgenological chest findings in terms of symptoms, clinical findings, pathological findings, and prognosis. Many of our roentgenologists are laboriously trying to master details of what are supposed to be pictures characteristic of certain types of pulmonary tuberculosis, without considering any basic reason for the production of these types. The variations are so numerous and changing that one would be kept constantly on the jump to keep a patient correctly tabulated. No one can be surprised at the controversies that are continually arising between clinician and roentgenologist. Certain broad principles will greatly harmonize the clinical and roentgenological findings. These principles today seem to offer the easiest explanation of events, and although future thought may evolve something better, we have at least a working hypothesis for the present. The more of the clinical and pathological side the roentgenologist knows, the better fitted he eventually becomes to interpret the roentgenographic plate. No one field of diagnosis is complete in itself although there is a high pro-

portion of cases where clinical methods alone suffice to establish a positive diagnosis, and again another high percentage of cases where the roentgenograph interpreted by a competent roentgenologist supplies evidence sufficient for a definite diagnosis. Then again we have a large group of atypical cases where the roentgenologist should be sufficiently skilled to combine clinical information and other features of the case with his roentgenological findings to arrive at the proper interpretation. When clinical and roentgenological findings all favor the same diagnosis we feel justified in making positive statements. There must be a limit to one's indecision, and contrary to the opinion of many the roentgenologist should avail himself of all clinical data.

My object here is to discuss briefly the value and limitations of the several methods of examination and explain the reasons for some of our roentgenographic and clinical manifestations. A number of factors enter into the consideration of the tuberculosis lung reaction and only brief references can be made without making this paper too voluminous. It has been shown experimentally (1) that the

first response to the tuberculosis bacillus invasion is the same as the response to any foreign body, and that in a few weeks the reaction takes on the reaction characteristics of tuberculosis. Tuberculous reinfections appearing subsequently to this are all modified in their character because of the previous infection. The initial and subsequent reinfections (unless overwhelming) produce a hypersensitiveness to tuberculo-protein which varies with each individual and with the age and extent of the lesions. This hypersensitiveness manifests itself by an exudation reaction about old and new areas of tuberculous involvement, when tuberculous reinfection takes place. The skin tuberculin tests usually show a marked reaction when hypersensitiveness or allergy is high, although experimental work recently done would indicate that the true allergic state may not manifest itself by the reaction to skin tests, and in these cases has been termed "latent allergy" (2). The focal reaction, however, is supposedly of fairly constant behavior under similar conditions. The body foci respond to reinfection exudatively or productively (fibrosis), like any inflammatory process the object of the reaction is supposedly protective in great measure. The infection is first corralled. If fibrosis predominates, shrinking avascular scar results. Without vascularity toxic symptoms must necessarily diminish. If there has been more of an exudative reaction, this exudate will gradually absorb in great part, caseocalcareous material may form, or we may have a tuberculous abscess with cavity result-

ing. In younger people the lymphatic system is generally more "open", as they have not been subject to so many lung infections, and the tuberculous infection may be kept in the lymphatic system (lymph follicles and nodes) which condition is usually well-borne by the individual in childhood, although primary tuberculosis of adult life is often very serious. Tuberculosis of the lungs involves the lymphatics or lymphoid tissue primarily and then spreads to the contiguous lung tissue. Phagocytosis is the means of removing bacilli into the lymphatic system from the surrounding lung tissue, blood channels, and air passages.

Allergy which determines in great part the tissue reaction or pathological activity is not the sole guide to immunity. It is well known that the various organs of the body may destroy tubercle bacilli without the production of any great local reaction. The "innate" immunity (3) of each individual varies markedly and is perhaps often the chief determining factor in the final outcome of the tubercle bacillus invasion. It is difficult to reconcile ourselves to opinions which ignore or belittle the idea of variations in "innate" immunity. Prognosis depends upon numerous factors which we cannot discuss here. It must be recognized that the exudative and productive reactions are what we attempt to determine both by roentgenograph and by physical examination. This however does not determine the whole story of a case. The future course of any tuberculous lesion cannot always be gauged by the existing pathological activity. A reaction benefiting

one case may be the cause of a fatal outcome in another, but we can always be sure that exudate means that the body is reacting to an irritant. This reaction may be stimulated locally or may be precipitated by more distant stimulants. These stimulants may be specific (tuberculous reinfection or tuberculin) or they may be non-specific (4). The non-specific stimulants or irritants may be organic or mineral substances, fatigue toxins, starvation, trauma, or may be non-specific bacterial infections, such as abscessed teeth, infected tonsils, etc. The reactivation by quiescent lesions can conveniently be explained on the theory of "balanced allergy" advanced by Victor Vaughan, (5) the specific predisposing cause of allergy being the tuberculo-protein of the tuberculous infection and the exciting cause being specific or non-specific, the tuberculous allergy in such cases by itself not being sufficient to precipitate a marked inflammatory reaction, but is capable of doing so under the influence of an added specific or non-specific irritant. Complete avascularization of the area would prevent demonstrable reactivation, and removal of either the exciting cause or the predisposing cause, as in other allergic diseases, would eliminate the reaction.

A healing lesion is accompanied by an increasing allergy and with this our immunity becomes increasingly greater. Like other infections complete cure is attended by a gradually diminishing immunity. A healed lesion of long standing may be accompanied by very little immunity, and the patient may again under conditions of

lowered vitality be liable to a reinfection. We all see repeated cases exhibiting widespread markedly exudative areas. It would seem logical to assume that these areas often represent a later stage in the reinfection. It is probable that the initial number of bacteria reaching the new lung areas of infection may be quite few, and unhindered by body resistance, develop rapidly and may be respread in various ways, amongst which may be through inhalation and through the phagocytic mobile large monocyte or endothelial leucocyte. By this time allergy, soon developed, comes into play to produce our exudative reaction. Animal experimentation showing the necessity of massive inoculation to produce secondary and tertiary reinfection does not consider the allergy of the animal at the time of inoculation which is probably high. We know that in humans, with high allergy, aspiration of a large amount of infected sputum into a bronchus will produce a reinfection with a most violent reaction (lobar pneumonia), but we hardly expect minute infections to gain much headway. Our initial allergy upon reinfection it seems would naturally determine in great part the extent of the involvement and subsequent inflammatory reaction. It would seem therefore, that one must consider both endogenous and exogenous sources of infection.

After the above brief summary of the tuberculous reaction which we find is dependent upon the hypersensitiveness of the individual and the vascularity of the infected area we may more readily inspect our methods of

investigating these local reactions. It is generally felt that chest findings can best be interpreted in terms of pathological activity or in other words "tissue reaction." We attempt to determine the degree and extent of this reaction. This reaction while important may be entirely lacking in many cases which may soon prove serious. We are often encountering cases where our first intimation of pulmonary tuberculosis is hemorrhage. We try to rule out all other possibilities (infarcts, mitral stenosis, malignancies, trauma, varices, parasites, etc.) and concentrate on finding an active tuberculous lung lesion. Maybe we obtain evidence of an old scar or retracted apex but we often cannot determine activity. A roentgenographic plate shows nothing and yet we feel certain it is due to active tuberculosis. With massive coagulation necrosis accompanying a markedly exudative reaction and cavity formation, hemorrhage or blood oozing may occur as we should expect, but this process is different. There is diminished allergy and with this a lack of immunity, and a very small tuberculous process involves a blood vessel with accompanying hemorrhage. It is probable that such erosion of very small blood vessels which should normally be most resistant tissue occurs as proof of lowered vitality and lack of immunity, and the patient must be considered as potentially serious, regardless of symptoms and other findings. One must not lose sight of the fact, however, that it may not require much of an altered lung condition to produce a pulmonary hemorrhage. The slight pulmonary congest-

tion in early mitral stenosis, for instance, is quite sufficient to produce hemorrhage. Miliary tuberculosis cases, in which we have great numbers of tubercles, rarely live long enough or are able to respond to the infection with enough developed allergy to produce a noticeable exudate as seen in the roentgenograph or microscopic section. With smaller showers of tubercle bacilli the process may limit itself to the region of the lymph follicles in the form of a peribronchiolitis, the infection not being overwhelming soon produces sufficient allergy to permanently prevent spread of the infection and soon leads to cure. It is the allergic response which determines in great measure the future course of the infection. Activity which we are unable to demonstrate clinically or roentgenographically does not, as we have just seen, justify us in completely ignoring the general condition of the patient, or treating the case as being in no wise worthy of special attention. Another somewhat similar condition is dry pleurisy. We may or may not elicit a friction rub and the roentgenograph may show nothing unusual, yet many of these pleurisies are the forerunners of more active tuberculosis.

In considering lung lesions which present evidence of an inflammatory process or "activity" we find a great deal of variation in the degree of so-called "activity." Our lesions may be so active as to produce symptoms and physical and roentgenographic findings which are difficult to differentiate from other acute non-tuberculous lung infections. Sputum examination, when positive for tubercle bacilli is often the only possible reliable clinical aid.

diagnosis, and roentgenographically one must wait until the lesions have had sufficient time to produce the usual characteristics of tuberculosis. A consideration to be kept constantly in mind is the individual "reaction factor" toward disease. No two people react alike to the same kind or degree of tuberculous infection, or any other kind of infection. We often see people actively at work, oblivious of anything wrong, come in for chest examination because of the knowledge that a "cold should not hang on so long", to find an advanced tuberculous condition present. Then again the patient may show marked symptoms with very few roentgenographic or physical findings. So many factors are concerned in the production of symptoms and findings that each case becomes individual in its behaviour. Clinical activity may bear no relationship to the severity of the pathological process. A quotation from an article by Medlar and Kastlin (6) perhaps puts this more comprehensively, "It is acknowledged that pathological activity does not mean a clinical or manifest disease in tuberculosis, but the common occurrence of a clinical breakdown after a clinical arrest of the disease would lead us to believe that pathological activity had not subsided with the abatement of clinical symptoms." The subjective feelings of the patient and the abatement of clinical symptoms are no doubt important in prognosis. In pneumonia our crisis which leaves our patient feeling better and on the highroad to recovery is accompanied by very little actual immediate alteration in the pathological lung condition. Tuberculosis however is a

slow-moving infection and recovery is gradual. The physician in his physical examination is attempting to determine pathological activity. Positive physical findings are important, but an absence of evidence of an active process may be most misleading. A subnormal temperature is common in many non-tuberculous individuals, an elevated temperature may be entirely lacking, an increased pulse rate is perhaps a better guide to activity but may accompany numerous other confusing conditions. Loss of weight, night-sweats, cough, fatigue, restlessness and irritability generally accompany outspoken cases, but an earlier diagnosis is most important. On physical examination, flattening of the chest wall, retracted interspaces, deficient expansion, lagging, etc., are all aids. Most of these physical findings may occur with emaciation from any cause. On palpation Pottenger's sign is too uncertain, vocal fremitus is of slight value, and our percussion note of no value in determining slight degrees of exudate as distinguished from healed fibrotic areas. The low spinal dullness and D'Espine sign, the only evidence one hopes to obtain in pure hilum node tuberculosis, is notably untrustworthy. With regard to auscultatory findings these rarely add anything of importance. Riles, the subcrepitant variety properly interpreted may be absent from even markedly exudative areas and when found may persist long after the pathological process has completely healed. It is for these reasons that we have been afflicted with our innumerable never-ending attempts to establish evidence of tuberculous activity.

ity by clinical and laboratory tests, the various tuberculin tests, the numerous clinical tests more recently advocated, the differential blood counts with relation to the predominance of large monocytes, lymphocytes, and Arneeth counts, the temperature and pulse reactions after exercise, etc. The "Sedimentation" test is finding too many exceptions to offer information that cannot be more certainly diagnosed by other means.

In discussing the roentgenographic findings I shall not describe the detailed anatomy of the lungs and minute accounts of the more recent theories and fine points differentiating tuberculosis from other diseases. I will just repeat that tuberculosis of the lungs occurs primarily in the lymphoid tissue of the lungs and may by extension invade the contiguous lung tissue. The exudate accompanying the inflammatory process is what determines the activity of a lesion on the roentgenographic plate. When the exudate completely fills one or more secondary lung lobules we have the so-called Dunham's triangle or fan. Different cases present different degrees of exudate about the foci of tuberculous infection. This exudate is determined by the inflammatory reaction which in turn depends in great part upon the patient's hypersensitiveness and the vascularity of the area. Fibrotic and other changes will affect this vascularity, which may go to complete avascularization and cure. The amount of toxic absorption taking place from completely fibrosed areas may be sufficient to give toxic symptoms when these areas are very large. Restimu-

lation of a previously infected area may be due to various agents described above. As the inflammation or activity subsides the exudate subsides. This is brought about in several ways, the avascularization of the area through fibrotic and calcific changes in the infected areas, and through digestion, reabsorption and neutralization of the focal products. The presence of exudate means that irritative products are still present and that avascularization through fibrosis is at least not complete. The beading and furring of markings speak for small amounts of exudate, while the large undemarked clouded areas represent the more marked exudates. The former tax one's knowledge of tuberculous infection. The various modifications and increase of lung markings accompanying different lung lesions are in a certain number of cases indistinguishable, but a very high percentage of these milder lung lesions are typical and can be diagnosed with certainty, qualitatively and quantitatively. A subsequent roentgenographic re-examination will clear up many of the previously doubtful ones.

The roentgenogram merely determines the degree and extent of exudate, which is just as true a measure of tuberculous activity as the reaction about any other kind of infection is a measure of the inflammatory process, or in other words it determines active pathology which may or may not have a corresponding clinical picture, which must necessarily be conjointly considered. Properly taken roentgenograms will rarely miss showing lesions which can be definitely shown clinically. Infraclavicular infiltrations which have



recently been so copiously described are difficult to find in any way other than roentgenographically. The presence of large calcific and fibroid areas in the lungs give undoubted evidence of previous tuberculous lung infection, although we frequently can elicit no history of anything suggesting such an infection. Tuberculous lesions do heal, even without medical advice, so that the mild forms can very often be diagnosed negative without doing any great harm to the patient. How many cases with slight afternoon rise of temperature and other indefinite symptoms can be positively diagnosed tuberculosis clinically? Tuberculosis is often diagnosed in these cases by a process of eliminating other diseases, basing the entire diagnosis on the fact that tuberculosis is so common. Gross autopsies will never be of service in helping to differentiate these very slight degrees of activity, and it would be too laborious to check up these cases with large numbers of serial microscopic sections so as to catch the proper areas. The presence of tubercle bacilli in the sputum rarely occurs in anything but lung lesions with gross roentgenographic evidence, and when found give no hint of their source. Even a gross lung lesion may frequently be continuously bacteriologically negative. It is true that exudate in a roentgenographic plate may be so slight as to represent activity of only academic interest, but it is always more satisfactory to make the diagnosis as fine as possible hoping that the physician in charge of the case will grasp the exact meaning of such degrees of activity. It seems almost pos-

sible at the present time to differentiate cases of mere reactivation, as determined by furring of old markings, from cases showing new areas of tuberculous involvement. The former may possibly be in great part responsible for many of our numerous easily controlled cases, as our superimposed irritant may be of an entirely non-specific and temporary nature. With regard to hilum tuberculosis of childhood there are numerous confusing conditions which produce hilum nodal swelling and unless we find undoubted evidence of tuberculosis in the lung parenchyma or other evidence of tuberculosis, such as tuberculous adenitis and calcified nodes, we cannot be certain of the condition. Poorly exposed films will often not differentiate between hilum calcifications and bronchial cross-sections. That all hilum node calcification must be tuberculous is still not definitely proven. We know calcific deposits in other locations may be of non-tuberculous origin (lime deposits in sheath of supraspinatus tendon, "subdeltoid bursitis", calcification of tumors, etc.)

#### SUMMARY

Much confusion exists in the interpretation of roentgenographic lung findings. Much of this confusion can be cleared up by learning the fundamental principles which are responsible for these findings rather than by trying to master pictures supposedly characteristic of different types of tuberculosis. We attempt roentgenographically and by clinical means to determine the same thing namely the 'activity' of a lesion. Exudate about a lesion signifies activity and this exu-

date depends in great measure upon the developed allergy. The individual "reaction factor" to disease is a most important consideration. As the activity or exudate subsides we find corresponding evidence in our roentgeno-

graph, which presents the actual pathological process to us. This evidence often cannot be obtained by other means. Numerous other factors must however, be also considered in prognosis.

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# Medical Management of Gastric Ulcer\*†

By G G RICHARDS, *Salt Lake City, Utah*

THE most important single factor in the treatment of a gastric ulcer is an accurate diagnosis. To subject a patient to a long period of careful dieting and control of his acid for an ulcer that does not exist is wasted effort and certainly not appreciated by the patient. To operate on him and perform a needless gastro-enterostomy is not to be excused. To attempt an ulcer cure medically for a malignancy of the stomach, whose only hope lies in surgery, will remain a face in the darkness of one's own conscience even after his mistake is hidden in the grave. Great responsibility, therefore, rests upon the clinician and the roentgenologist who first make a diagnosis of an intragastric lesion, and secondly differentiate a benign from a malignant ulcer.

For many years we, at the Salt Lake Clinic, have been ardent admirers of the Mayo Clinic. Naturally, we became their disciples in the fear of the relationship between gastric ulcer and cancer. Consequently, we have, in the past, almost always recommended that gastric ulcers be treated surgically.

Our complications, however, from partial gastrectomies or other operative procedures, sufficiently radical to completely remove the ulcer, were frequent enough to make us feel that the dangers attendant upon such opera-

tions might be greater than the probability of the ulcer being or becoming malignant in carefully selected cases.

Acting upon this thought, the medical department of our Clinic became courageous about two years ago and decided to treat medically all cases of ulcer of the stomach in whom we could not find any definite evidence of the lesion being malignant. We argued that a three weeks delay before resorting to surgery would not be very serious and that medical and dietetic management during this period would probably improve the condition of the patient even as a preoperative measure and that we could use this as a sort of therapeutic test. We assumed that a benign ulcer would show definite signs of improvement clinically and from an X-ray standpoint, while an ulcer that was already malignant would refuse to respond so favorably.

Our courage was also supported by the fact that some of our most authoritative pathologists have expressed themselves that there is very little danger of a benign gastric ulcer becoming malignant and that Dr. McCarty of the Mayo Clinic may be mis-

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taken in the interpretation of his so-called cancer cell

The only dangers attached to such medical treatment, we felt, were

First, that of the ulcer becoming malignant

Second, that of perforation or hemorrhage which occurs less frequently during proper management

During the last two years we have had twenty-four cases of gastric ulcer under observation. Of this number, ten were operated because of a history of massive hemorrhage, or perforation, or because the X-ray examination was quite suspicious of a carcinomatous ulcer.

Of the remaining fourteen patients, eleven were treated medically, seven in the hospital and four as ambulatory cases. Three cases refused treatment and were lost track of.

The medical management was preceded by removing all focal infections.

When possible, they were kept in bed most of the first two weeks. If in much pain associated with tenderness, heat was applied to the abdomen. In those cases with marked pylorospasm and retention, belladonna was used.

The free acid of the stomach was fairly well controlled in most of the cases by the use of the alkalies, soda bicarbonate, calcium carbonate and magnesium oxide. We have followed the suggestion of Crohn and others, using small doses, five to ten grains, one or two times between the feedings. We are thoroughly convinced that this method of using from 60 to 120 grains of alkalies, in the twenty-four hours, has distinct advantages over the large doses formerly prescribed by Dr

Sippy, principally in that the small frequent doses do not cause alkalosis or a reaction rise in the production of HCl in the stomach as occurs after the ingestion of large doses.

Determinations as to the control of free acid were made by stomach aspirations at various times in the twenty-four hours.

We feel that the pyloric sphincter is probably the most important factor in the production and control of hyperacidity, because it determines the emptying time and regulates the regurgitation of the alkaline duodenal contents into the stomach.

The nervous system is certainly largely responsible for the pyloric action. This is often demonstrated by the difficulty experienced in controlling the gastric acidity and the ulcer syndrome in patients burdened by worry, fatigue or nervous excitement. Relief of these conditions is very important. Sedatives may be necessary at the beginning.

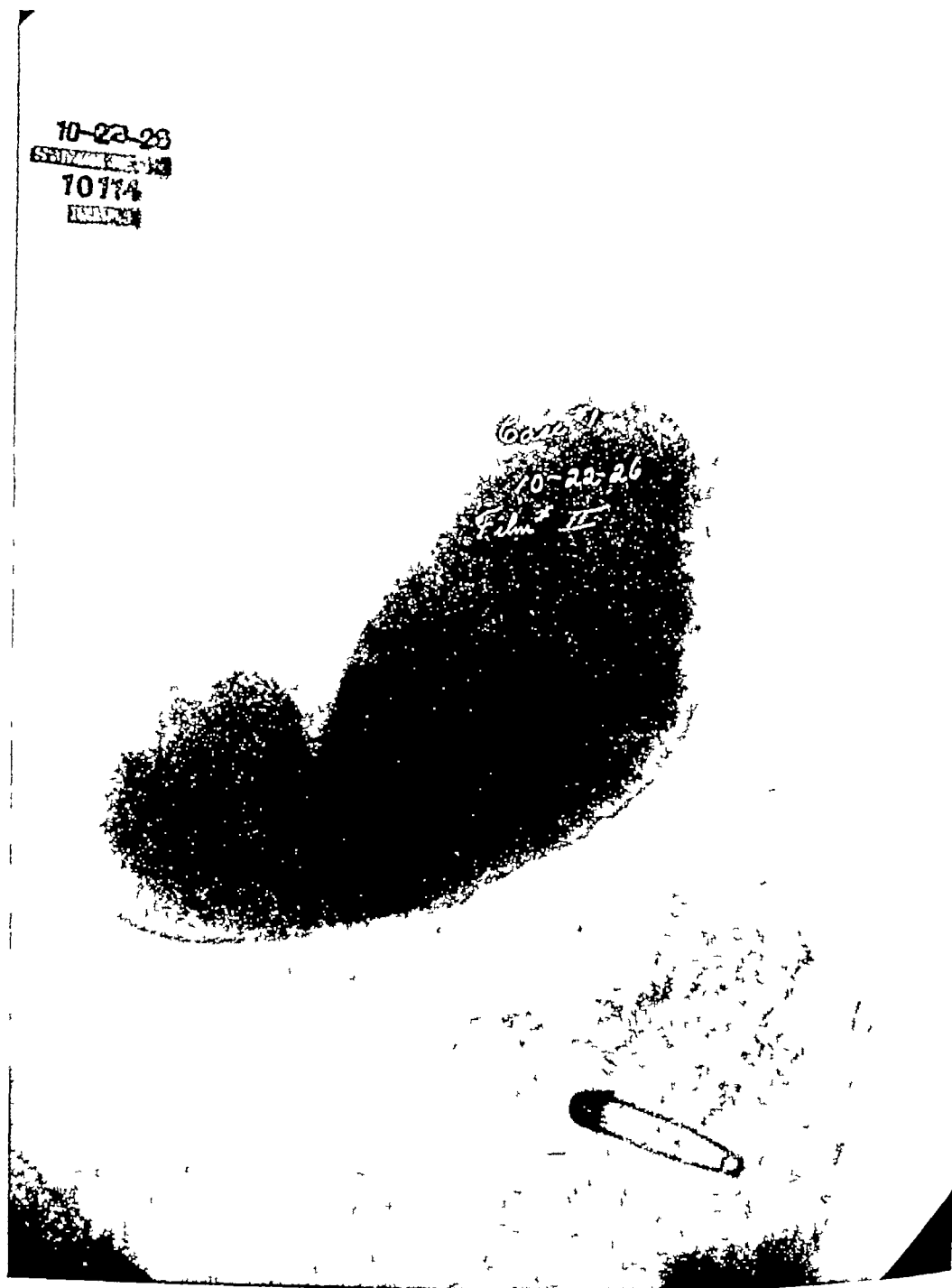
The diet which we have used is a modified Sippy type. It has been our experience that a careful diet is necessary for six months to a year and that it is never safe for an ulcer patient to become careless with his diet. In order to insure the cooperation of the patient, he must first be educated to the reasons and necessity for this prolonged dieting. Second, the diet must be sufficiently nourishing, simple and convenient to enable him to make a living and enjoy life while on it.

The continuance of the frequent milk feedings is probably the most important single factor in the diet of these patients.

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CASE 1 FIGURE 1 Showing the ulcer before treatment



CASE I FIGURE 2 Showing the crater entirely gone seven weeks after beginning of treatment

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CASE 1 FIGURE 3 Shows no sign of a return of the crater three months after treatment



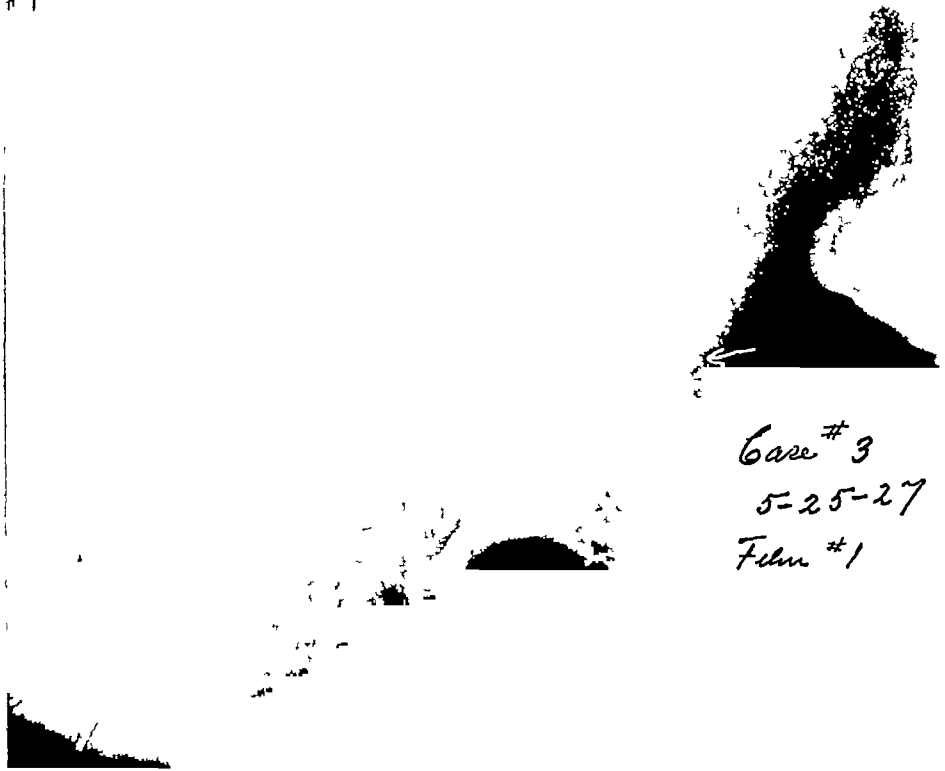
CASE I FIGURE 4 Shows a perfectly normal stomach thirteen months after beginning treatment, during which time this patient has gone through a normal pregnancy





CASE 2 FIGURE 1 Shows a very large crater at the beginning of treatment

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CASE 3 FIGURE 1 Shows a large crater with a very broad base at the beginning of treatment

We have attempted to re-examine all the cases about every two weeks during what might be called the probation stage of this medical management

#### TREATMENT OF COMPLICATIONS

##### *Hemorrhage*

Mild bleeding is very common in gastric ulcers. It does not require special treatment unless it persists after a week of diet and medical management.

Acute profuse hemorrhage calls for immediate and very definite measures. Lowering of the blood pressure suddenly often is very effective in helping the physiological processes to stop the bleeding. Instead of placing the patient in a reclining posture, support him in the upright position until he faints, then slowly put him to bed and keep him as quiet as possible. A blood pressure apparatus may be applied to each extremity to reduce the amount of blood in the abdomen. A hypo of morphine is very necessary as a sedative to the nervous system and particularly to the peristalsis. It should be repeated every six to eight hours as necessary during the first twenty-four hours.

An ice bag over the epigastrium may have some specific beneficial effect or it may help merely by making it necessary for the patient to remain quiet in order to keep the bag on his abdomen.

If nausea and vomiting persist, stomach lavage done very carefully is advisable. A small catheter stomach tube can be inserted just within the cardia and not cause gagging or any

traumatism to the ulcer. Sometimes a solution of 1 1,000 ferric chloride seems to have a definite beneficial effect. Some advise leaving one dram of 1 1,000 adrenalin chloride in the stomach after the lavage, but I am always afraid of the reaction rise in blood pressure after adrenalin.

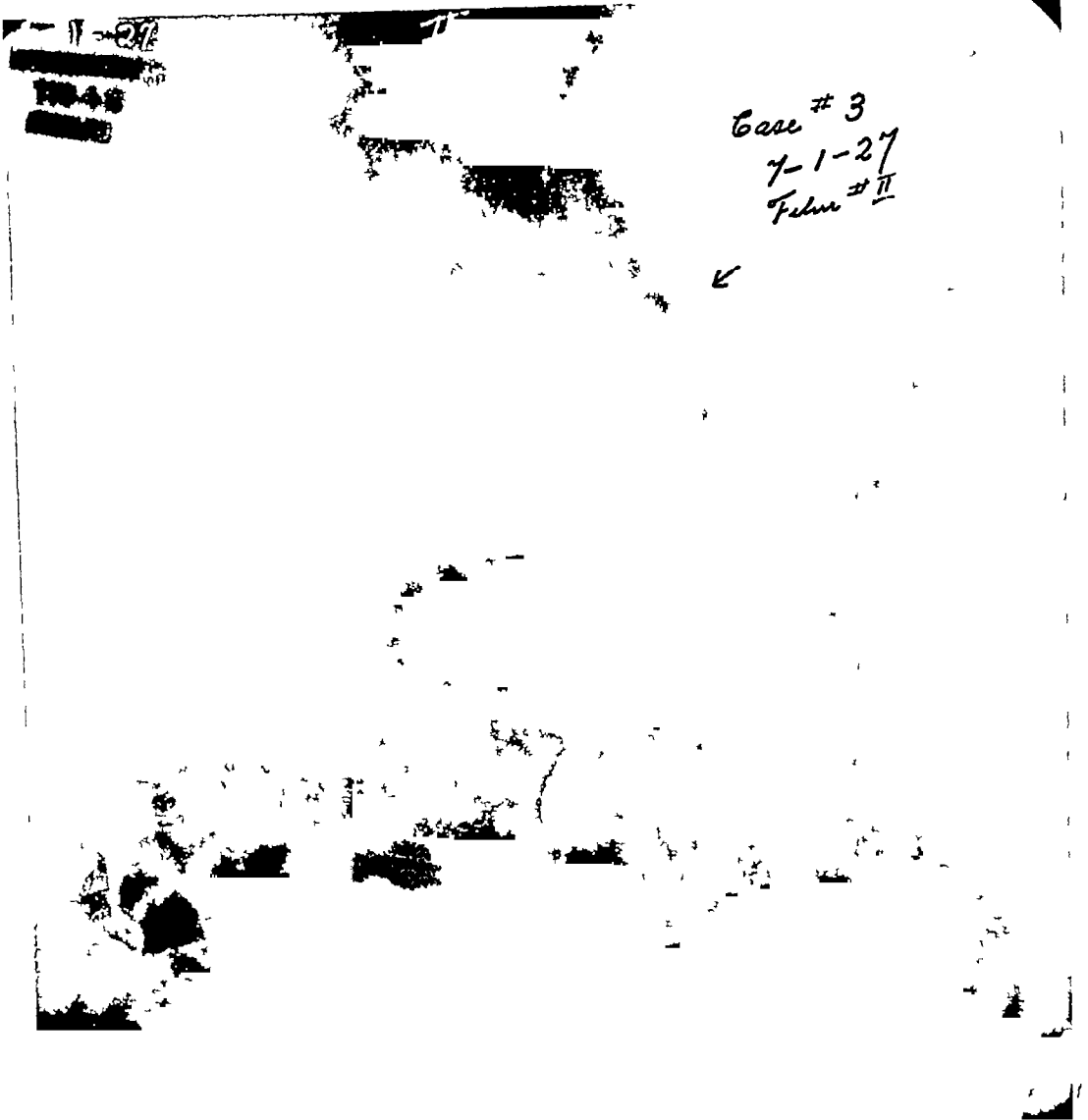
The volume of blood must be restored to the patient. Just how this should be done will depend upon the severity of the hemorrhage. As a rule, normal saline and glucose by bowel or occasionally by vein are sufficient. Some cases require immediate transfusions because of the amount of the loss. Smaller quantities of blood, 300 c.c., repeated if necessary are safer than large amounts.

Patients who have had a tendency to repeated small hemorrhage are greatly benefited by transfusions. Some cases, with anemia following a hemorrhage, do not recover well upon the usual medical management. A transfusion will often act as a splendid tonic and start them on a more rapid road to recovery.

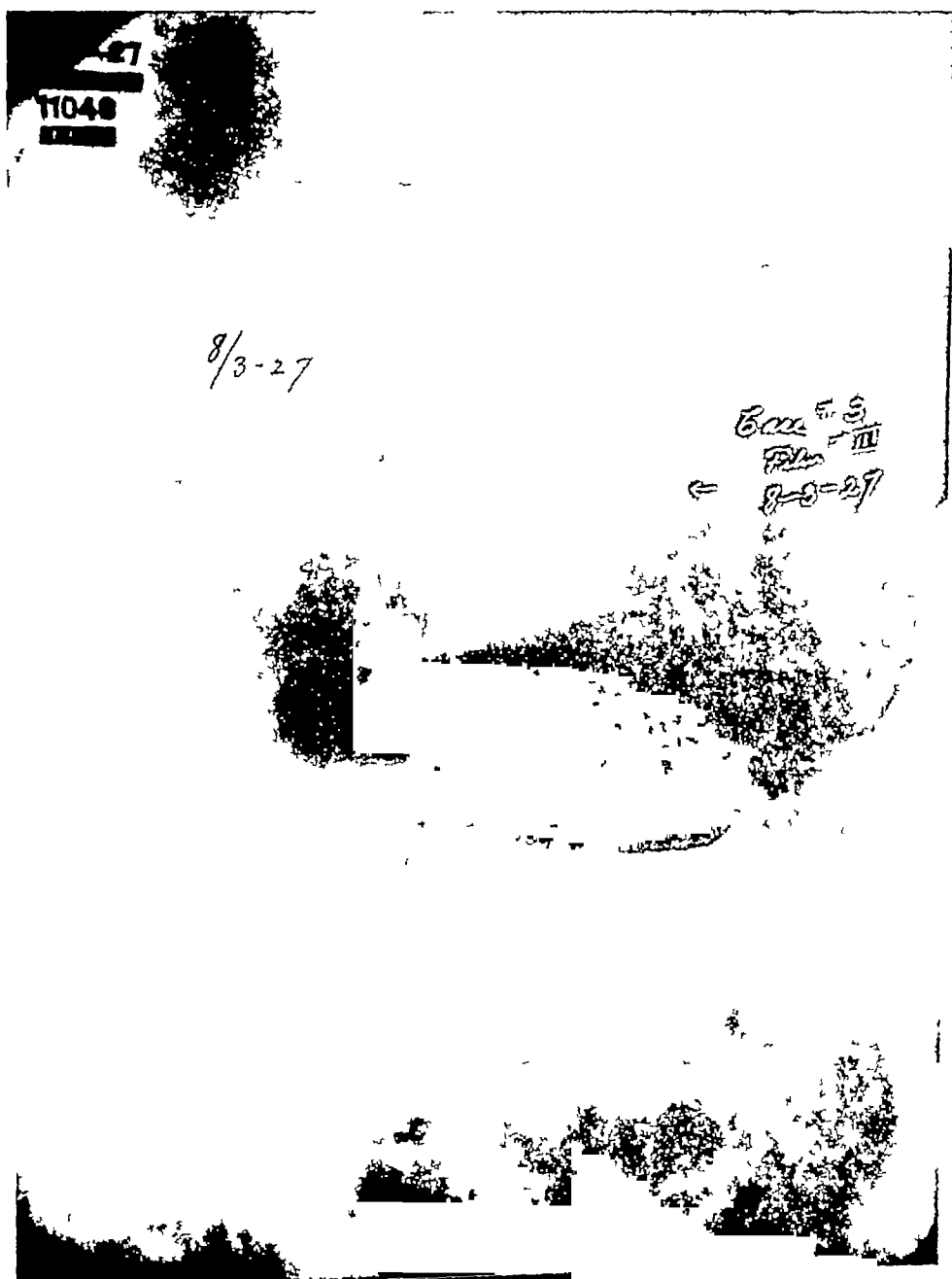
We have never found any coagulant as efficient in promoting clotting as the injection of whole blood either into the vein or subcutaneously. Occasionally calcium intravenously has seemed to be of benefit.

##### *Feeding a case after a hemorrhage*

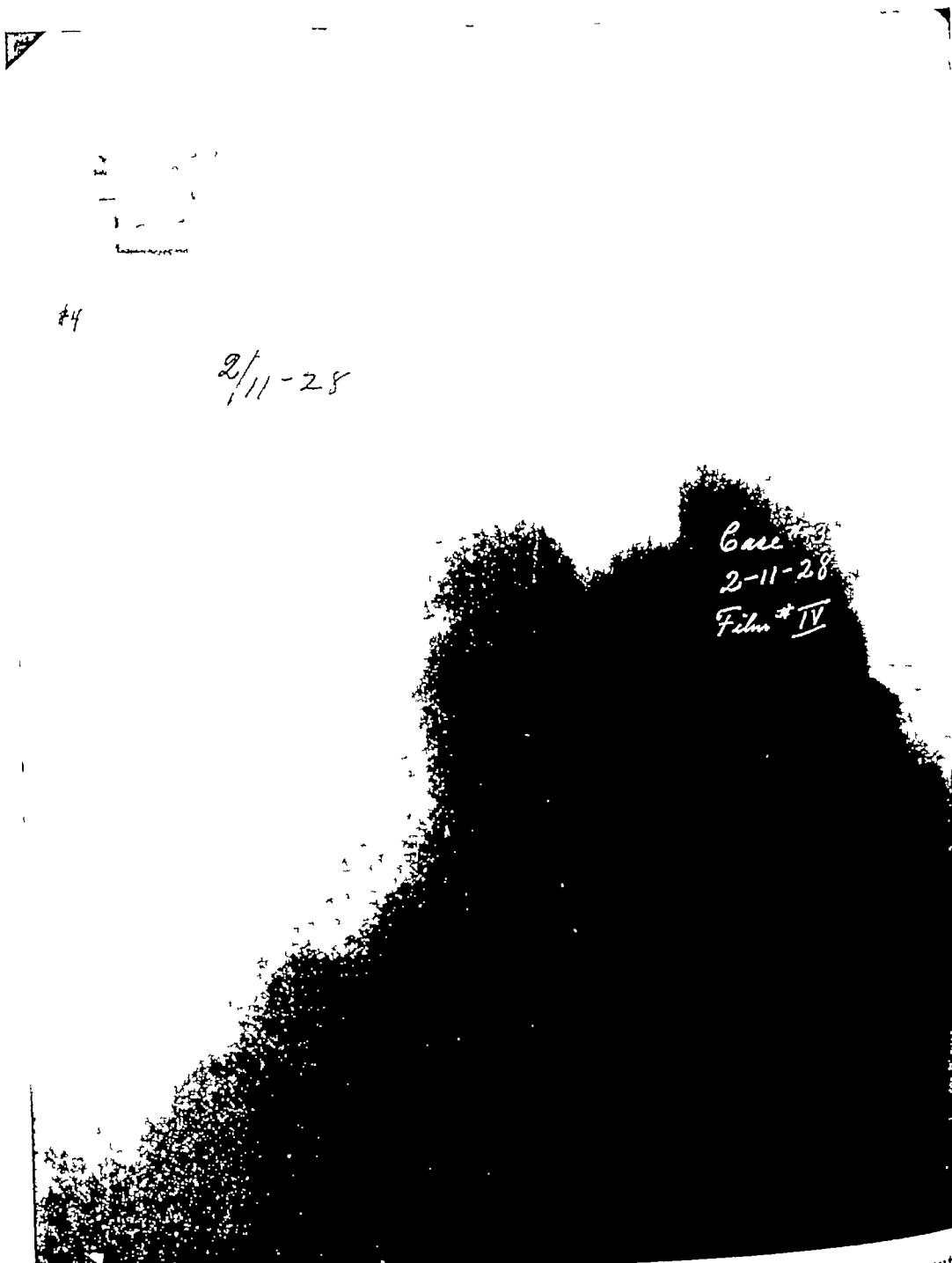
Everything by mouth is withheld for twenty-four hours. Water in one ounce doses is then begun every one-half hour, increasing to two ounces on the second day. Milk  $\frac{5}{11}$  and lime water  $\frac{5}{11}$  every two hours is given on the third day and is increased each day.



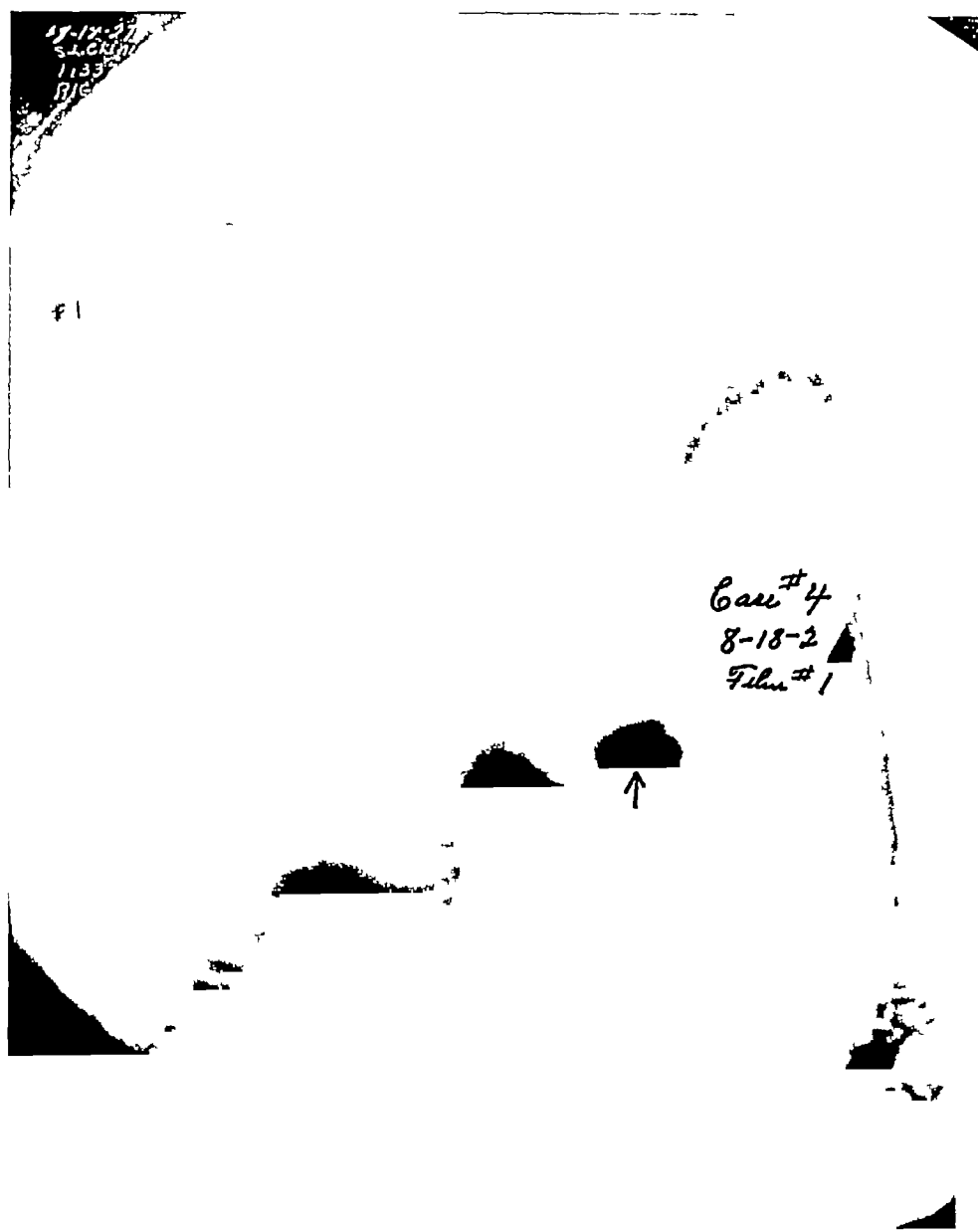
CASE 3 FIGURE 2 Shows the crater only about half its original size five weeks after beginning treatment



CASE 3 FIGURE 3 Shows the crater almost entirely gone nine weeks after beginning treatment



CASE 3 FIGURE 4 Shows no sign of a crater nine months after beginning treatment



CASE 4 FIGURE 1 Shows a huge crater at the beginning of treatment

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Case #4. Figure 2. Shows this crater entirely gone nine months after treatment. At present in the first month when he had a severe gastric hemorrhage all infected teeth were removed and he made rapid progress.



-16-27  
11222  
#1

Case #5  
8-16-27  
Film #I

CASE 5 FIGURE 1 This patient had a perforated pyloric ulcer six years ago resulting in the above deformity. The gastric ulcer is apparently of recent origin.



CASE 5 FIGURE 2 Shows the gastric ulcer entirely healed but medical treatment did not influence the obstruction and deformity at the pylorus

until the usual medical diet for ulcer is attained

Operation during or immediately following a profuse hemorrhage is certainly to be avoided, except in cases where all possible medical help has failed and the condition is alarming

#### *Gastric Ulcer with pyloric obstruction*

The treatment of this condition depends upon the degree and character of obstruction and upon the presence or absence of toxemia. Mild obstruction will usually yield to the medical management and belladonna. If the obstruction does not so respond, the case should be referred to surgery. These cases usually have definite symptoms and changes in blood chemistry indicative of a toxemia. This is especially true if they have been taking large amounts of alkalis. Their symptoms vary from loss of appetite, headache, drowsiness and nausea to extreme restlessness, muscular irritability or even tetany. The urine becomes scanty and contains large amounts of albumin and casts and it can easily be mistaken for a nephritic urine.

Blood chemistry reveals an alkalosis with a  $\text{CO}_2$  combining power sometimes up to and above 100—a high urea and a low chloride.

Recognition of this condition should be made early and immediate treatment begun. It consists in stopping the alkalis immediately which, by the way, should be given with very great care if at all in cases of definite pyloric obstruction. Infusions or enteroclysis or both, of a five or ten per cent glucose and one percent salt

should be given immediately and daily in amounts totalling 2500 cc to 3000 cc. The infusions of glucose must be given very slowly or a large part of it will be lost through the kidneys. Insulin can also be given to aid in the utilization of the glucose.

The stomach should be carefully emptied each morning and evening.

The diet should be of such nature as will remain liquid while in the stomach as soups, gruels, orange juice, *Jell-O*, custards, etc.

#### *Perforation as a complication*

Many gastric ulcers show a tendency to perforate. If the perforation is acute and complete, immediate operation is imperative. If it is incomplete and chronic, as many are, the same medical management as before outlined may be tried.

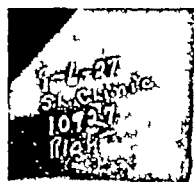
The summary of the results of treatment in this group is as follows.

Only two subsequently came to operation, one a foreigner who failed to remain on a diet after leaving the hospital. The other was a very neurotic maiden lady of fifty-four years whose many idiosyncrasies toward food made a proper diet impossible. Two of the group died, but neither from their ulcer. One case, a man (E P) a miner, aged sixty-eight died from a severe pulmonary fibrosis and a degenerated myocardium. The other a man (E O) age sixty-two died with uræmia from a bad nephritis and a decompensated endocarditis.

Our results have been based upon the subsequent clinical history and X-ray findings.



CASE 5 FIGURE 3 Shows the stomach after a partial gastrectomy with no sign of return of the gastric ulcer



#2



CASE 6 FIGURE 1 Shows a small crater at the beginning of treatment

1. 10  
2. 10  
3. 10  
4. 10



CASE 6 FIGURE 2 Shows no signs of the crater four and one half months after treatment

25 2  
11654  
JUN 1967



Case #7  
11-23-27  
Film #1



CASE 7 FIGURE 1 Shows a very deep crater at the beginning of treatment



CASE 7 FIGURE 2 Shows only partial healing of the ulcer. This patient was not seen between the dates of these two X-ray films and remained on a cereal diet but a short time. He did however, take alkalis during this period.



We failed to get temporary improvement in only one case, the maiden lady above mentioned

We have had mild relapses in four cases, which could be attributed to dietetic indiscretions or mental worries

We have not regretted any attempt which we have so far made. We have not included in this list any of the cases in the last six months, so we feel reasonably safe that none of these ulcers were malignant. We hope that future developments will not make us feel that we have been fool hardy in this medical treatment of some ulcers of the stomach when such an institution as the Mayo Clinic recommend surgery in all cases of gastric ulcer.

#### CONCLUSIONS

I This experience has convinced

us that in some properly selected cases of ulcer of the stomach, medical treatment is justifiable

2 These cases should be under close observation and have rechecks at frequent intervals

3 Benign gastric ulcers, in our experience, respond more readily to medical management than duodenal ulcers and are less apt to have resultant deformities

4 So far, we have seen no evidence of malignant degeneration in any case

The accompanying X-ray films are self-explanatory. They belong to a part of the group in whom the X-ray pictures best illustrated the lesion. The remaining cases, not here illustrated, showed equally satisfactory results.



Two animals constitute too small a series on which to base definite conclusions regarding the lethal dose of a poison. Furthermore Gil y Gil overlooked an important complicating factor. The smaller rabbit had intravenously 5 cubic centimeters of carmine and the larger animal 7 cubic centimeters of the dye after the sublimate injection. Suzuki's protocols show that the former died shortly after the carmine injection and that the latter became so weak within four hours that it was killed. The relatively sudden exitus strongly suggests an embolic death. In my experience the injection of such quantities of carmine has more than once been the cause of death in poisoned rabbits. Forbus (6) has likewise found that rabbits are invariably killed by large injections of carmine. Granting that Suzuki may have been more fortunate than others in this respect the fact remains that a complicating factor was introduced and one cannot be certain whether death was caused by the mercury or the dye.

Barbour's sole purpose was to test the efficacy of an antidote for mercuric chloride. Furthermore he introduced the poison intravenously instead of subcutaneously and the doses were based on 1 kilogram body weight rather than 2 kilos as given in the passage quoted.

Nakata's study was primarily concerned with the pathologic stages of the sublimate kidney in the human. For the purpose of comparison rabbits were given sublimate in quantities corresponding according to body weight with that taken by the human cases.

In most instances the dosage in rabbits was considerably greater than 0.0035 gm per kilogram of body weight.

Gil y Gil did not himself study the pathologic changes in the acute sublimate kidney but quotes the descriptions of Suzuki who found in two rabbits after subcutaneous administration of 0.003 and 0.006 gm of sublimate a well marked necrosis of epithelium in the distal and transitional segments of the proximal convoluted tubules. He emphasizes that the amounts capable of producing such damage were administered subcutaneously and that he has given much larger doses intravenously to nearly all rabbits in his series.

The conclusion that renal immunity to mercuric chloride may be experimentally demonstrated is based on the study of nine rabbits. No definite plan of experimental procedure was followed with the exception of time intervals between injections. The irregular manner in which all animals were given both subcutaneous and intravenous injections renders difficult any reliable interpretation of results. Further important information may be gained from the discussion of the microscopic findings in each animal.

**Rabbit 1** Necrosis of all except first part of proximal convoluted tubular epithelium, no increase in connective tissue. The author rightly does not claim that immunity was shown in this case.

**Rabbit 2** No demonstrable changes in any tubular cells, hyperemia of glomeruli, glomerular epithelium uninjured. Gil y Gil seeks to explain the marked difference in the kidney of



time was allowed for complete cellular regeneration

Rabbit 7 Fresh degenerative changes in the epithelium generally. The quantitative estimation of mercury excreted after the last injection of 0.01 gm gave 0.005 gm and for this reason the kidney was believed to be immunized. This in spite of the microscopic evidence of widespread cellular damage

Rabbit 8 First and second divisions of proximal convoluted tubules uninjured, some necrosis in distal division. Following the final injection of 0.05 gm between 0.0042 and 0.0045 gm was excreted in the urine during the first three hours and the kidney was therefore believed to be immune. When we remember that the selective action of mercury is in the segments of the proximal convoluted tubules, in which the author has described necrosis, it is difficult to believe that any immunity was shown in this instance.

Rabbit 9 No claim is made for immunity.

The author does not state whether or not the intestine was examined in any of the animals. The stain for hyaline droplet degeneration was done in but one instance and was negative.

In order to compare the excretory ability of the kidney in non-immunized and immunized sublimate animals a normal rabbit was given 0.005 gm of mercuric chloride subcutaneously and the urine collected by catheter for eight hours. In the first four hours there was no excretion while in the second period 0.001 gm was excreted. From this the author concludes that in non-immunized animal the rate and

quantity of excretion is appreciably decreased. However if we compare this result with those obtained in the so-called immune animals it will be found that Rabbit 5 given 0.01 gm intravenously excreted about one-third of this amount in three hours, Rabbit 7, with 0.01 gm subcutaneously excreted one-half the dose, but not until twenty-four hours had elapsed, while in Rabbit 8 which had received 0.05 gm subcutaneously excreted only about one-eleventh of this amount within three hours. Comparative results are of value only when the dosage and time have been identical.

In summary Gil y Gil states that the experimental results with sublimate corroborate those obtained with uranium. With sublimate it was also possible to build up a remarkable resistance of the tubular apparatus by reason of which the poisons will be, in contrast to non-immunized animals, excreted more rapidly and in greater quantities.

It is obvious that not a single case is convincing and above criticism. In the few instances where immunity was possible the results are questionable on account of the long periods of time elapsing between the last administration of sublimate and the examination of the kidney. The quantitative analyses are of little value as proof of immunity for reasons pointed out above.

#### AUTHOR'S EXPERIMENTS

In view of Gil y Gil's failure to determine the lethal dose of sublimate and his error in its computation from the work of others it was deemed necessary to establish this point before



tubular epithelium Three were studied, seven, nine and seventeen days respectively, after administration of the poison All showed high grade parenchymatous degeneration of the tubular epithelium but little actual necrosis In the glomeruli aside from slight swelling and sometimes desquamation of epithelium covering the tufts nothing was observed except congestion of the vessels

With higher dosages (0.015-0.02 gm) definite necrosis of cells in the distal and transitional segments of the proximal convoluted tubules occurred The affected segments are found here and there in all zones of the cortex with many still escaping injury At this stage (2 1-2 to 4 days) practically all cells in the divisions affected by the sublimate are dead, for the most part desquamated, and forming loose casts at the site of injury and in the upper part of the descending limb of Henle The few nuclei still present are markedly pyknotic A distinct difference is noted in the appearance of some of the dead cells in the mercury kidney from that seen in the uranium organ in that their morphology is fairly well preserved and the cytoplasm has a distinctly hyaline appearance Most cells however break up into finely granular debris Fat in the necrotic cells is less constant than in uranium nephritis The epithelium of the first and second divisions of the proximal convoluted tubules shows parenchymatous degeneration The glomerular vessels are moderately congested, no apparent change is visible in the epithelium of Bowman's capsule, but not infrequently the covering epithelium of the tufts desquamates

In the capsular space some albumin is often present but blood is rarely seen Cystic intraglomerular hemorrhages, so common in the acute uranium kidney, occurred in only three of the thirty six cases studied Two of the three animals had received large intravenous injections of sublimate Hyaline droplet degeneration, also common in the uranium kidney, was rarely observed in the acute stages although in one animal having 2 milligrams of mercuric chloride intravenously these bodies were fully as abundant as in any acute uranium kidney All others were negative In the tubular epithelium this form of degeneration was noted in five instances where death occurred in the acute stage of poisoning Calcification of casts was observed in three of twelve rabbits dying from the effects of the first injection the earliest appearance being the fourth day

#### *Regeneration of epithelium*

This begins rather constantly on the fourth day The new cells are in all respects similar in appearance to those found in the uranium kidney, namely, elongated flattened cells with hyperchromatic nuclei and bluish-pink staining cytoplasm One important difference is however not uncommon, in the uranium kidney most of the dead cells quickly break up and form granular masses which are soon swept out of the tubules but in the sublimate kidney, not a few cells undergo a hyaline change and remain in the lumen of the affected segments Often such cells are still present when regeneration begins and the protoplasm of the new cells quickly pushes between the old





istration may be very slight if the degree of kidney damage is a reliable criterion. This is particularly well illustrated by one of the rabbits in the writer's series. The animal received 0.004, 0.008, 0.016, and 0.032 gm of sublimate over a period of 63 days and was killed 3 days after the last injection. Examination of the kidney revealed only a few tubules with regenerated epithelium, for the most part there was only well marked parenchymatous degeneration and but little actual necrosis. The marked local reaction at the sites of injection and the extensive intestinal lesions found at autopsy in this rabbit were much more severe than those in the kidney. In contrast to this and indicating further the variability in absorption of sublimate may be mentioned the finding of a definite chronic nephritis in another rabbit of the same group which had almost the same quantity of sublimate.

The numerous and serious objections to sublimate just cited makes it impossible to speak with certainty of an acquired immunity of renal cells for this substance. The findings in a few animals in which immunity is possible may now be discussed.

**Kidneys** combined weight 20 gms. The capsules strip with slight difficulty exposing cortical surfaces which are in general pale but show also moderate numbers of petechiae. The surfaces are smooth in places, finely granular in others. On sectioning considerable resistance is encountered but there is no gross evidence of lime salt deposition. The cortex is pale and at the junction with the medulla there is slight scarring.

#### MICROSCOPIC

Zenker-formalin fixation, hematoxylin and eosin stain. When the number of proximal convoluted tubules showing recent necrosis of epithelium are compared with the same tubules lined by regenerated cells it is apparent that more damage has resulted from the last dose than all previous ones combined. The lumina of the segments last damaged are packed with desquamated necrotic cells. Regeneration has not yet begun. Casts are very numerous in the Henle's tubules and collecting ducts. None of the casts contain lime salts. In the cortical zone nearest the medulla many of the transitional divisions of proximal convoluted tubules are lined by regenerated epithelium but this is true to a much lesser extent in the intermediate and outer zones of the cortex. The new cells are flattened or irregular in outline with dark bluish-pink staining cytoplasm and hyperchromatic nuclei and often forming giant cells or containing in the cytoplasm the remains of dead epithelium. In some instances the pinkish-staining debris is disappearing leaving large vacuoles which may contain finely

Rabbit 2 0.002 S					
9-21-26	wt	1200 gms	given	0.002 gm	HgCl <sub>2</sub> per kilo subcut
10-21-26	"	1490	"	double initial dose	0.004 gm
11-22-26	"	1800	"	second	0.0080
12-13-26		1690	"	third	0.0162
1- 3-27		2040	"	fourth	0.04
104 days					

Died 3 days after last injection. Total 107 days.

#### Autopsy

Weight 1650 gms. Dry gangrene at site of fourth injection. No ascites or hydrothorax. Marked diphtheritic colitis.

granular brown deposit. The regenerated cells show no evidence of injury. This is stained for fat with Schärlach's dye and a considerable amount of fat is



jection and the excretion by way of the intestine it was not considered worth while to attempt to estimate the quantity excreted by the kidney. That part of the last dose in each instance reached the kidney is evidenced by fresh necrosis of original but not the regenerated convoluted tubular cells, indicating increased resistance on the part of the latter. The degree of this resistance is unknown. Had all the last mercury given reached the kidney this would be sixteen times the original dose in the first rabbit and eight times in the second animal, but we know from the intestinal and local lesions that such was not the case.

Tolerance of the whole organism for mercuric chloride is very limited, in most instances being only about twice the subcutaneous lethal dose. This is in marked contrast to the results obtained with uranium for which a tolerance of thirty-two or forty times the lethal dose was frequently attained.

In only one animal in the sublimate series was a truly chronic kidney lesion obtained. The microscopic picture in this instance was very similar to that of a chronic uranium kidney, showing great reduction in the number of original proximal convoluted tubular cells, extensive regeneration, considerable interstitial scarring and pigment deposition in the regenerated cells. The glomerular capsules were thickened, the Bowman's membrane epithelium hyperplastic and forming epithelial crescents and even obliteration of the capsular space. This animal received four intravenous injections, beginning with 0.0018 gm and ending with 0.0144 gm. Unfortunately death occurred within a few minutes after the

last injection, and, although the original epithelium shows parenchymatous degeneration and even early necrosis it was thought advisable to exclude the animal from the immune series because of the short time the poison could have acted. The case is of value, however, to show that sublimate also produces chronic glomerular as well as tubular lesions in spite of the fact that in the acute stage glomerular damage is less constant and less marked than in uranium poisoning. Hyaline droplet degeneration in the glomeruli is not common in either the acute or subacute sublimate kidney, occurring in only seven of the thirty-six animals of the series. In the damaged convoluted tubular epithelium this form of degeneration was observed in twenty-one of the thirty-six kidneys. Fatty degenerative infiltration in living cells and casts was noted in twenty-six instances. In the living cells fat is present in about the same quantity as in the uranium kidney but in less constant and not so abundant in casts.

Fatty degenerative infiltration was observed in the liver only four times, extensive in one, slight in the others. The constant relationship to dosage seen in uranium animals is lacking.

## CONCLUSIONS

1. Local corrosive action and irregularity of absorption after subcutaneous administration the danger of thrombosis following intravenous injection and the excretion by the intestine resulting in severe enterocolitis makes sublimate an undesirable substance to use in the experimental pro-



# Etiology of Backache in Medical Practice\*

By GEORGE L. LAMBRIGHT, M.D., F.A.C.P., *Cleveland, Ohio*

WHEN I was asked to discuss backache from a medical standpoint it was understood that the discussion was to be limited to those aches which are experienced in the lumbar and sacral regions. My remarks will be confined to this locality.

Backache, like headache, fever, and blood pressure is a symptom, and may require considerable investigation on the part of the physician before its cause is ascertained. All of us realize that there are a large number of causes. Fortunately other symptoms are commonly associated with backache which make it appear at once only incidental to the condition. We should always think of backache in this manner. As one limits his practice the importance of his specialty is likely to dominate the etiology, thusly at one time the gynecologist believed most backaches were due to pelvic disorders, the urologist that most were due to kidney diseases, the orthopedists held that they saw a lot of backache from strains, osteal conditions, and malformations of the spine, and we in medicine are sure that most are due to infectious states. No doubt we are all correct as each sees that which he specializes in and finds backache associated with it.

It is very important that we famil-

iarize ourselves with all of the possibilities that will be mentioned here tonight, and be prepared to make those investigations that are necessary to make a final diagnosis before attempting to institute measures of relief. One should have a workable outline in mind when a case of backache comes to him for solution, and a classification as follows will be helpful: 1st—Backaches from systemic diseases, 2nd—from local conditions, and thirdly from reflex conditions. Systemic conditions are a reason for the majority of backaches seen in the general practice of medicine, and acute and chronic infectious states hold first rank, with metabolic disorders, coming in for consideration quite frequently. The backache from an acute infection, as tonsillitis, or grippe, is easily recognized. Those due to chronic foci of infection, on the other hand, are sometimes very difficult to locate. Blood diseases, syphilis and some of the metabolic states as hypothyroidism may require some study before one can say definitely that they are the cause of the backache. After one finds a condition, and it is corrected, it may take some time to prove that it was the cause of the backache. Some of the most stub-

\*Internist's discussion of backache before Cleveland Academy of Medicine, February 1925.



The patient examined for pains in the lower part of the back should be completely undressed, and the posture carefully noted. Often round shoulders, protuberant abdomen, and the relaxed condition of the musculature will be valuable points. The lordotic back should always be looked for. The tension of the muscles over the lumbar region should be noted, as here resides most pains from infections and strains. A careful palpation of the sacroiliac joints and lumbar nerves should be made. Valuable information can be obtained by deep abdominal palpation with thoroughly relaxed abdomen. In a properly relaxed patient firm pressure through the abdomen will locate sensitive nerves which cannot be located otherwise. While making this examination a floating kidney, or chronic appendix can be recognized. A pelvic examination will give information regarding tumors, and position of the uterus. Infections of the adnexa may be discovered. An examination of the prostate in the male, and sometimes its secretions for evidence of chronic infection may be necessary. One should not neglect to make an examination of the rectum for tumors and hemorrhoids. In many cases it is necessary to make radiographs of the teeth and sinuses. A careful examination should be made of the tonsils. It is important to know the condition of the arterial and respiratory systems, as conditions therein may be the sources of infection or chronic fatigued states. A urine examination should not be neglected, as often microscopic blood or pus may give a clue to the cause. Some of the local causes of backache are not discovered until an X-ray examination is made

with a Bucky diaphragm. We have had three cases of calcified retroperitoneal glands which were tender on palpation through a relaxed abdomen that would have escaped discovery without the assistance of the X-ray. It can readily be seen by the remarks on physical examination that it must be thoroughly done. One should not haphazardly have all the examinations made which have been mentioned, but should judge which studies are necessary after the physical examination. One who makes a diagnosis of backache from X-ray or local examination may be misled. In no field of medicine is the knowledge of diagnosis so necessary. Root pains of luetic crisis, diabetic neuritis, myelogenous leukemia, and osteitis deformans (Paget's disease) are some of the causes that I have seen of backache. Sharp shooting pains occurring every day at about the same time, or with change of position, coming on and remaining for two or three weeks at a time, and then disappearing without any apparent reason, may be radiculitis. I have seen two such patients, and one has had this condition of affairs for forty years. The urologist sometimes surprises you by what he finds by pyelography.

The reason why the cause of backache is not discovered more often is on account of the lethargy of ourselves. We realize that it is not often serious, and do not investigate thoroughly. There is no doubt that this symptom interferes with the welfare of almost as many people as does head ache and it should not be neglected. About one-tenth of our patients who are studied for chronic disease complain of backache.





tion and vasectomy prove beyond question the power which these glands, at least, have in influencing psychic development and change. Other equally convincing evidence has been submitted by Cushing, Dercum, Kanavel, Goetsch and others as regards the pituitary, while the psychic relationship of thyroid and pancreas has become so well-known as to require no further comment.

It is quite true that our knowledge of symptom-complexes is not yet adequate to enable us to definitely fix upon the exact gland or glands involved in many cases. It is equally true that while a single gland may be primarily involved in many instances, these manifestations are invariably to be attributed to a derangement in varying degree and proportion, of the whole endocrine system. For this reason it should always be borne in mind that when we speak of the thyroid as the causative factor in a given condition, or the hypophysis, or the testes, we mean that the single gland mentioned is apparently of primary importance, but that other glands are likewise involved, very possibly as causative factors. Among these groups are especially those cases classed as mongols, traceable apparently to thyroid dysfunction, cretins, which I believe are, basic to the thyroid disturbance, of hypophyseal origin, and the various gonadal dysfunctions. Of these groups, the first two at least, and the last, probably, in addition to the physical variations which make possible the diagnosis, each falls within a fairly definite range of mental development, which appears likely to prove

as definitely symptomatic as is the physical complex.

In a series of twenty-one cretins which I examined, after eliminating those cases of a distinctly debatable type, I found the intelligence quotient of these patients to vary between the limits of 35 and 65 (Binet). On the whole, the average for this group was somewhat nearer the higher limit. The cases of mongolism of which 38 were examined, were of a definitely lower order, their range being between an I Q of 15 and 45 and the average tending toward the lower limit. In addition to their falling into what may be accused of being a somewhat academic grouping, each individual of each of these types evidenced a considerable number of reflex actions which are not far from identical for all of those patients grouped within the class. Further than this is the notable fact that their responses given to the tests used to ascertain the mental age were very similar for all of the individuals falling within a given diagnostic group. That is, cretins will not only show an I Q within the designated limits for their group, but their responses to the various parts of the tests will be very closely similar for all. The same statement applies with equal force to mongols, and insofar as one is able to group them into fairly definite endocrine classes to the parathyroid dystrophies, adrenal dystrophies and possibly other groups even less definitely classifiable.

It is in the class of sex-gland dystrophies that some of the most surprising results are obtained. One would expect, I believe, that precocious



castration in the female. The exact relationship existing between the ovaries and mental deficiencies is not clear. It is surprisingly true that the hermaphroditic type of female frequently appears to possess a marked libido with very little or no restraint. This is probably not a true libido, but is due to a coincident greater aggressiveness, rather than to other causes. The frequent tendency of these cases toward homosexuality would tend to bear out this belief. On the whole, my observations upon female defectives would lead me to believe that generally, the lower the mental type, the weaker is the libido in a given individual. In many ways, the other possible effects of the ovaries upon the psyche parallel closely those of the testes in the male. In both sexes, the statement that a high degree of sexuality is apt to accompany advanced mental attainments and psychic virility may be, I think, safely projected. Stockard believes that a great deal of confusion has arisen in judging this subject, due to the fact that what is really a type of exhibitionism—a sort of defense reaction, is frequently mistaken for advanced libido but is really evidence of a low degree of sexuality. I am quite certain that promiscuity is no criterion of sexuality, but is more often merely an evidence of weak mentality.

As additional evidence is advanced which enables us to more accurately mark out the limits of the various hypophyseal dystrophies, these begin to reveal striking and rather characteristic variations. As regards thymic dystrophies, the same situation governs which we find in the gonads. One can never be quite certain where the

effect of thymus ends, and that of hypophysis, thyroid, gonads or adrenals begins. As for the pancreas, the mental characteristics of advanced pancreatic diabetes are familiar to all, as is probably the fact that there is a distinct line of demarcation between pancreatic diabetes and the diabetic conditions of an apparent hypophyseal origin.

While the line between mental subnormality and insanity is a particularly distinct and well-marked one, it has been demonstrated that in many of the dementias, as well as in feeble-mindedness, there is present a well-marked and clear-cut variation from normal in the condition of most of the glands of internal secretion. In such psychopathic cases, which condition takes precedence in either time or etiology, I have not the temerity to suggest. The mere fact of their coincidence, does, it seems to me, carry a definite suggestion when viewed in the light of such effects in other and better known conditions.

In summary, a majority of the endocrine dystrophies present marked and definite psychic symptoms peculiar to their class. It seems probable that both somatic and psychic symptom-complexes are the result of endocrine disturbances, acting upon the entire organism, including also the other glands of internal secretion. It is probable that still deeper than these hormone effects are other more obscure causative factors, which through the glands of internal secretion affect the entire organism. It is obvious that the manner in which many experimentally produced endocrine variations affect the organism is a close parallel to many





des 7re

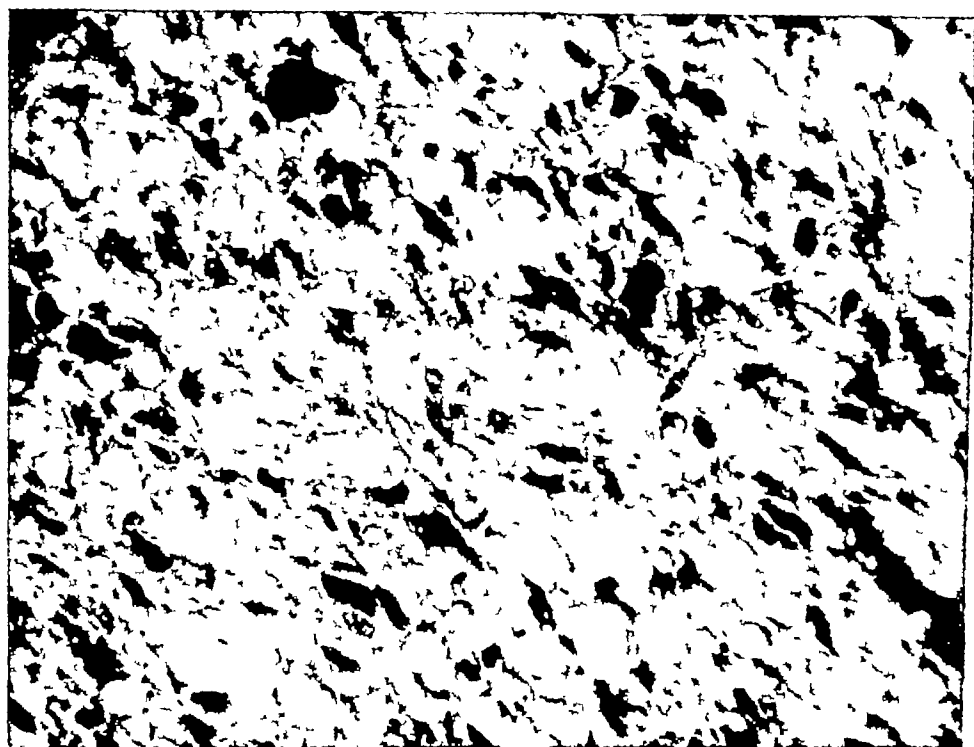


Fig. 1—Longitudinal section of right cerebral hemisphere showing tumor mass of centrum ovale of right parietal lobe.



2—[Longitudinal section of right cerebral hemisphere showing width of st. p. of tube & miss implicating the extreme end of the dot & limb of the tube involved & vent. of surrounding white matter of parietal lobe.





3—High power photomicrograph showing the various types of cells in the tumor. Bipolar spongioblasts. A few larger cells somewhat resembling astrocytes. Stroma much vacuolated.

absent on the left side but present on the right. The organic reflexes are controlled.

*Laboratory Examinations* RBC 5,330,000, WBC 8,600, Polys 57%, Lymphos 43%. Blood Wasserman and spinal fluid negative. Urine examination—Sp Gr 1.020, reaction acid, sugar negative, albumin—very faint trace, mucous shreds excess, casts—few, dye test 50% excreted in 1st hour and 10% in 2nd hour, test day—night specimen urine 97 cc—1.020, 10 A M 74 cc, 1.019 12 45 P M 91 cc—1.011, 3 15 P M 120 cc—1.010, 5 P M 50 cc—1.022. Spinal fluid under slightly increased pressure, cells—5 small lymphocytes per cm globulin  $\chi$  gold curve showed no change in color.

#### SUMMARY OF THE SUBJECTIVE NEUROLOGICAL SYMPTOMS AND FINDINGS

Six months previous to entrance to hospital, patient began to suffer with

at first severe frontal headaches, great general weakness, numbness of left leg and several weeks later numbness of the left arm, this was followed by slight weakness and later paresis of left leg and arm dragging and circumduction of left lower extremity slight lower facial and left lingual paralysis. Examination showed slight diminution of tactile but definite diminution of the temperature sense and hypoaesthesia of the left arm and leg with definite ataxia and stereognosis slow celebration without aphasia, intact cranial nerves, no optic edema or papillitis negative spinal fluid under slight pressure, with slowly approaching coma and death.

From a careful study of the above



mal, the corpus striatum or optic thalamus showed no change. Sections through the left hemisphere, crura, pons, cerebellum and oblongata macroscopically appeared normal.

The tumor on section diffusely invaded the surrounding tissue and showed many degenerative changes. The cells of the neoplasm vary a great deal in size, shape and staining properties, many being bipolar and of spongioblast type, others apparently unipolar and still others larger and

more of astrocyte type. Mitotic figures are numerous. The stroma consists of the glial processes of the tumor cells and of thickened capillaries which are very numerous. The vessels show marked hyaline change and also adventitial proliferation. Hemorrhage, cystic and anemic degeneration are present in many parts of the growth. The tumor agrees with the usual description of the spongioblastoma multiforme.







In Testimony whereof we have subscribed these presents with our names, and caused our Seal of Incorporation to be annexed

Done at Poughkeepsie this Sixteenth day of July 1816

Seal Attest JOHN THOMAS, President  
JOHN BARNES, Secretary

Agreeable to the By-Laws of the Medical Society of the 20th Medical District of the State of Ohio Charles P Livingston is admitted a Member of Said Society

ORESTES J E HAWLEY, President

It was at the Beekman Street home that Drake with Halleck wrote the verse satires that appeared in the New York City Post under the title of the Croaker Papers. For a considerable period the authors were unknown even to Coleman the editor of the Post. Most of their work has been forgotten as it owed its popularity largely to local knowledge of characters and circumstances but at the time it attracted wide attention. Our modern "Columnists" are the nearest approach to this type of journalism and are the lineal descendants of the "Croakers."

In 1816 Drake published his best known poem, "The Culprit Fay," and in the same year he married the daughter of Henry Eckford. The impetuous young doctor was at once raised to a position of relative financial ease. He continued the practice of his profession, but seems to have given most of his time to social and literary activities. He was young, good looking, and a poet, three of the best credentials to any society and to them were added a playful, kindly and affectionate nature that quickly endeared him to associates.

In 1818 he visited Europe with his young wife. His health began to fail after his return and as symptoms of pulmonary disease appeared he was advised to spend the winter months in a milder climate. Drake showed little concern regarding himself and it was with difficulty that he was persuaded to follow a dietary regime or take any regular treatment. He did, however, spend the winter in Louisiana but tuberculosis had gained such headway that after lingering through the following summer growing weaker and weaker he died September 21, 1820, being but 25 years of age. Thus he became one of a great company of youth and genius.

Possessed of some strange spirit of fire,  
Quenched by an early death

Dr. Drake was but a minor poet judged by the verse he left though it was of such a character as to promise greater things. 'The Culprit Fay' was his most ambitious effort. It contains little more than six hundred lines and is noteworthy in that for the first time American scenes were considered as worthy of description in verse. The scene of the poem is on the Hudson in the vicinity of West Point, and the following is a fine example of a poetic description of moonlight on mountain and river.

'Tis the middle watch of a summer night—  
The earth is dark but the heavens are bright

The moon looks down on old Croquet  
She mellows the shades of its grassy breast,

And seems his large grey form to throw  
In a silver arc on the wave below

This is almost a splendid example of versification as Melles notes





# Editorial

## SOME PHYSIOLOGICAL EFFECTS OF GOLF

Karpovich in the American Physical Education Review for November, 1928, has reported the results of an investigation as to the physiological effects of golf, which should be of great interest to the many medical players of this game, not only to its possible effects upon themselves but also with reference to its effects upon their patients. There are very few physicians, who today are not confronted with the question of advising patients either to play or not to play golf. When as is usually the case the patient is advised to play unexpected sequelae not infrequently happen, and when they forbid the game the patient usually plays anyway again with results that are often very different from those predicted. There is really nothing in the literature that is helpful in respect to the physiological or pathological effects of golf. Most of the literature as to the effects of golf is mere guess-work written from the standpoint of enthusiastic rooters for the game and concerned chiefly with its recreational aspects. In the very few books treating of golf from a medical standpoint it has been chiefly from the point of view of the utilization of the game in the treatment of neurotic or mentally abnormal individuals. But for the far greater number of normal individuals and those physically handicapped by

organic lesions of heart, bloodvessels, kidneys, etc., there is no information available as to the advantages and disadvantages attendant upon golf playing. Golf has become extremely popular in this country during the last ten years, as is shown by the great increase in both private and municipal golf courses, and in the very large number of players. With all of its popularity opinions on the game differ widely. On the one hand we hear the game derided as fit only for old people and for the middle-aged who are beginning the descent of life. An "old ladies" game it has in the past been frequently called by the younger devotees of tennis and the more active sports. It is true that in any country club one sees a large proportion of men past the peak of life belonging to the tired business or professional man class, but on the other hand the game is rapidly being taken possession of by the younger generation who claim that the real game of golf can be played only by youth. Striking proof of this contention is shown in the fact that the real golf champions belong to the younger set of players. On some links the older men are finding themselves in the way of aggressive youthful golfers. Golf is attracting a high school adolescent and a tremendous number of young people to our links. And then there are the deaths of old people on links from heart failure and



study threw no light upon this question. When the diastolic pressure was lower in the standing position than in the reclining position the examiner usually found some permanent or temporary lesion, such as intoxication, neurasthenia or heart disease. Schneider's index is an expressive index of condition, being greater in healthy people, and smaller in diseased people. People with heart disease or other lesions show a great fluctuation. People with thorough compensation show the least fluctuation. The test appears to be the best one to ascertain cardiovascular adjustment. It seems possible also to say that the greater the fall in the Schneider index the greater has been the demand upon the cardio-vascular system. From an increase in heart rate and a decrease in Schneider's index we may assume that the volume of circulation per minute is increased. The examiner found a decrease in pulse pressure after a game. The more exhaustive a game the greater was the decrease. It has been suggested that the pulse pressure times the pulse rate might serve as an index of the volume circulatory blood or circulation rate. On the basis of this study the  $PP \times PR$  may be used as a group index, but it did not bear out the idea that it is an exact index of the circulation rate. The study did suggest that if there is big drop in  $PP \times PR$  that the blood circulation is inadequate. It is important to test the  $PP \times PR$  in a standing and not in a reclining position immediately after the game. Based upon the study of individual cases it seems possible to draw the following conclusions. The great variability in Schneider's

index in one and the same person may serve as an index of the variability of the cardiovascular conditions. A great drop in the usual pulse pressure in the standing position may indicate disturbance in circulation due to fatigue. If, in spite of an increase in the pulse rate in a standing position, there is a marked decrease in  $PP \times PR$ , there is also indicated a disturbance in cardiovascular adjustment, which in most cases is coincident with well pronounced subjective feelings of fatigue, or of feeling "not well". Alcoholic intoxication and loss of sleep preceding the game causes a great drop in pulse pressure in a standing position after the game and lowers the endurance. In case of myocarditis there is very little change in all items after an easy game for half an hour on a small course. More prolonged games, and on longer courses, cause a marked drop in systolic blood pressure and pulse pressure, and usually the subject does not feel well. Three thousand yards of playing makes very little difference to a healthy man, when he plays with the same tempo all the time. Hearts with valvular lesions, but well compensated, react in the same way as sound hearts after a mild exertion. A strenuous game, as in tournaments, may cause a more rapid pulse on the next morning and a lower  $PP$  in the standing position. A more friendly game has less effect on pulse rates and pulse pressure than a championship game. The heart rate increases and the  $PP$  decreases more in the latter case. In prescribing the game for patients it is safe to begin with the half-hour game. 71



45 and 60 years of age—a successful business or professional man, who rides to and from his place of business every day, and who religiously plays golf once or twice weekly, thinking he is exercising to the good of his body, when in reality the manner and degree of this exercise is doing him positive harm. Before going upon the links he fortifies himself—the worst possible thing for him to do, in its effect upon his cardiovascular system—by a nip from his flask, and on coming in, red, perspiring, with a cyanotic hue to his floridness, with dilated cutaneous vessels, and increased heart rate—he, feeling

more or less “all in”, resorts to another nip, and then usually follows this with a beefsteak supper. This is the material from which the deaths on the links and in the club houses are recruited, golf when taken in this fashion predisposes to acute cardiac dilatation, coronary thrombosis and apoplexy. Golf is a fine game when played right—as a social, leisurely game, without strenuousness or the excitement of competition, when taken otherwise it becomes a very dangerous form of exercise to individuals of the successful, over-prosperous, arthritic type of build and constitution.



of heat. Evidence is given that the addition of saponin produces an appreciable increase in the conductivity of an electrolyte. Its use is, therefore, contraindicated when electrical measurements are being made on biological material. The currents used in diathermy behave as do high frequency currents of the pure sine wave form in respect to their passage through biological material.

*Observations on Some Cardiac Lesions Coincident with Pulmonary Tuberculosis*  
By I. D. Bronfin and Saling Simon  
(Amer. Rev. of Tuberculosis, December, 1928)

The coincidence of valvular heart disease and pulmonary tuberculosis is not as rare a condition as is generally supposed. Dyspnea out of proportion to the pulmonary involvement, especially when there are no constitutional symptoms, should arouse the suspicion of an existing cardiac affection. The absence of murmurs does not exclude the possibility of grave valvular affections. According to Broadbent a murmur is rarely heard in the third stage of mitral stenosis. It is of particular importance to the phthisiologist to remember that digestive disturbances, pressure pain in the epigastrium, gaseous eructations followed by temporary relief from the epigastric distress, paroxysmal attacks of dyspnea and cough, fatigue on the slightest exertion, disinclination or inability to concentrate on a physical or mental effort, and other well-known so-called neurotic symptoms, may be due as much to early cardiac decompensation as to active pulmonary tuberculosis. The proper evaluation of these symptoms is no small problem. The incidence of valvular heart disease in pulmonary tuberculosis, recognizable clinically, is only about 6 per cent in their experience. Artificial pneumothorax, when indicated in such cases, should be administered with great caution. The earliest manifestation of cardiac disturbance is an indication for discontinuing the pulmonary compression. Complete bed-rest must be rigidly enforced for a longer period of time than in cases not complicated by heart disease. The electrocardiogram is often of the greatest

value in determining the course of obscure cardiac symptoms.

*The Preventorium Child: A Clinical Review of Three Hundred Cases*. By I. D. Bronfin (Amer. Jour. of Dis. of Children, November, 1928)

Clinical records of 300 preventorium children were reviewed, and a study made of the roentgenograms. An underweight of 7 per cent or more was found in 70 per cent. In 30 per cent fever was a prominent symptom. An appreciable difference was not observed in the symptomatology or physical signs between the tonsillectomized and the nontonsillectomized groups. The greatest incidence of clinical disease and positive physical signs was noted in those with a history of definite exposure. Physical signs were often negative when the history and symptoms pointed to active disease. The x-ray was of the greatest aid in diagnosis when correlated with the other symptoms. Of the entire series, only seventy-two roentgenograms of the chest were considered within the normal. Calcification at the hilum, strongly suggestive of tuberculosis, was observed in only 22 per cent, but it is believed that the incidence would have been greater if films in the oblique position had been taken. Primary foci were detected in 11.6 per cent and in 11.3 per cent there was noted a frank parenchymal pulmonary infiltration. Attention is called to the difficulty of making a diagnosis of tracheobronchial tuberculosis which in this series was frequently responsible for active symptoms and was often attributed to other causes. Under treatment symptomatic improvement invariably occurred. Unrelenting supervision was necessary, for in many patients there was a recurrence of symptoms with increased physical activity. A notable recession was not noted in either the cervical or the tracheobronchial glands after prolonged periods of continued lehoterapy. Bronfin concludes that active juvenile tuberculosis is still unrecognized in the majority of instances and that physical signs of juvenile tuberculosis are delicate and of misleading value. The history and symptoms are more important as a basis for treatment than are physical signs. The x-ray is of





are absorbed from the intestinal tract. This report is primarily concerned with the hepatic lesion, but it may be noted briefly that some of the dogs had convulsions, tonic and clonic, and some became comatose. The development of these conditions depended on the dosage. Sections of the kidney in some animals showed lesions similar to those found in humans dying of eclampsia. The author believes that his findings explain in a measure why the hepatic lesion in eclampsia can be averted by limiting the protein intake of the patient in the last months of pregnancy.

*Clinical and Pathological Changes in Livers of Copper-fed Animals* By William C. Von Glahn and Frederick B. Flinn (Proc. of the Soc. f. Exper. Biol. and Med., December, 1928, p. 200)

A study of the chemical and pathological effects of copper on the liver was made on a series of guinea pigs, albino rats and rabbits. Different groups of matured Belgian hares, kept on a standard diet of hay and oats, with cabbage and carrots on alternate days were fed daily doses of various copper salts. In each of the rabbits, yellow or yellowish brown refractile pigment was found in the liver cells. In some, pigment was also present in phagocytes in the portal areas and occasionally in connective tissue cells in the same region. In a few animals some of the endothelial cells of the sinusoids contained pigment. Iron was not found in the pigment, which stained with fuchsin,

but not with Sudan III, Scharlach R, nor with osmic acid. Nile blue sulphate colored the pigment greenish blue to deep blue. The amount of connective tissue in the portal areas varied in different portions of the same sections and in different animals, but was nowhere sufficiently developed to justify a diagnosis of cirrhosis. The amount of copper in the livers showed considerable variation even in the same group, though in general the livers of those animals receiving metallic copper had the largest amounts. Livers of rabbits dosed with sodium acetate contained pigment which had the same staining reaction as in the copper fed animals, the livers of normal rabbits contained pigment and identical variation in the quantity of connective tissue in the portal areas as were observed in copper fed rabbits. Rabbits fed carrots alone showed a marked increase in the quantity of pigment over that present in the piece of liver removed before the animals were kept exclusively on a carrot diet. Rabbits on a carrot diet did not show an increase in the pigment when fed copper over that observed in rabbits which were kept on carrots for only 14 days. Turnip-fed rabbits also showed a small amount of pigment. The results on guinea pigs and albino rats were entirely negative. From the above experiments it was concluded that copper does not cause pigmentation or cirrhosis of the livers of rabbits, rats or guinea pigs and that the pigment found in the liver of rabbits is probably of exogenous origin.



geons and radiologists. For the researcher engaged in this line the very full bibliography is an important and valuable feature of the book. The illustrations are satisfactory, and the printing excellent.

*William Harvey* By ARCHIBALD MALLOCH, M.D., (McGill), M.R.C.P. (Lond.), Librarian, N.Y. Academy of Medicine. 103 pages, 10 full page plates and 3 text illustrations. Paul B. Hoeber, Inc., New York, 1929. Price \$1.50.

This delightful little account of Harvey's life by Malloch is reprinted with corrections, from *The American Journal of Surgery* (New Series, Vol. V, Nos. 3 and 4, September and October, 1928). It originated as a tercentenary address delivered at a joint meeting of the Harvard Medical Society and the Boston Medical History Club held on the twenty-fourth of April at the Peter Bent Brigham Hospital. It is hoped that medical students, doctors and others will welcome a sketch of the life and work of one of the greatest scientists and physicians, and that they will be stimulated towards further reading of these fascinating subjects, the history of science and the biography of its great men. An attempt has been made in this sketch to show how a knowledge of the circulation was painfully and slowly won in the centuries before Harvey and exactly how the latter arrived at the important conclusion that the blood moved in a circle. In this Malloch has been particularly successful. The contents of the chapters are given to a consideration of the following: Harvey's education, a day with Harvey, publication of the book on the circulation, Harvey's predecessors, the movement of the heart, the circulation, further proofs, tour on the continent and return to London, the witches, another continental tour, civil war, Oxford, London, the book on generation, Harvey and the College of Physicians, his death, burial and will. The illustrations comprise the title page of the first edition of "*De Motu Cordis*", Harvey's *Stemma* at Padua, the anatomical theatre of Fabricius at Padua, Harvey's pointer or wand, Harvey demonstrating to Charles I his discovery of the circulation of the blood,

Edward's engraving of William Harvey, Harvey's letter to Lord Dorchester, Title Page of first edition of "*De Circulatione Sanguinis*", Frontispiece of first edition of "*De Generatione*", engraved title page of Elzevir edition of "*De Generatione*" with London imprint, portraits of William Harvey and Hempstead Church. The story of Harvey's life is concisely told by Malloch in a pleasant conversational manner. One gets from it a very living impression of Harvey's times, education, method of delivering lectures and the ordinary routine of a day in Harvey's life. The speculations concerning the printing of the book on the circulation, as to why it was printed and published in Frankfurt and by Wilhelm Fitzer who never published any other important medical or scientific book, are just sufficiently touched upon as to excite the reader's interest in the problems of the first publication of the great book. The chapter on Harvey's predecessors is a well-accomplished bit of condensation of an enormous mass of available material and those on the movement of the heart, the circulation and further proofs, give the essence of Harvey's great discovery, told in an original and pleasant manner. The story of Harvey's connection with Lancashire witches shows his independence of minds and freedom from the superstition of the times. This is a pocket book that every practitioner should own and carry about with him until he has made the story of the great discovery and the great discoverer his own intellectual property.

*Laboratory Diagnosis and Experimental Methods in Tuberculosis* By HENRY STUART WELLS. The Johns Hopkins University and Hospital. With a Chapter on Tuberculo Complement Fixation by J. Stanley Woolley, Locum Sanatorium, Locum, New York. Introduction by Allen K. Krance. The Johns Hopkins University. 333 pages, 25 illustrations. Charles C. Thomas, Springfield, Illinois-Baltimore, Maryland, 1928. Cloth \$3.50. Keratol \$1.25.

This book has a twofold purpose. It aims to describe the more important methods of the laboratory diagnosis of tuberculosis and



gating the dynamics of the heart and circulation has not been extensively employed. It may be safely asserted that the number of investigators can be counted on the digits of two hands. It is, therefore, the author's hope that aside from its use as a reference medium and its value as a review of the subject, this little book may encourage others to enter this fascinating and precise field of investigation. Chapter I is concerned with the evolution of graphic methods for registering pressure pulses, Chapter II with the registration of pressure curves by micro-manometers, Chapter III with the configuration of pressure pulses in the cavities of the heart, Chapter IV with sequence of cardiodynamic events as established by pressure pulses from the auricles, ventricles and the aortae, Chapter V with the arterial pulse, Chapter VI with the venous pulse, Chapter VII with the consecutive phases of the cardiac cycle and the criteria for this precise determination, Chapter VIII and IX with the response of the heart to physiological variable, Chapter X with the intimate character of the ventricular contraction and Chapter XI with the pressure pulses under certain abnormal types of ventricular contraction. There follows a bibliography and an index. This little volume succeeds admirably in the presentation of the facts concerning the pressure pulses and in the evaluation of the experimental results. The book is an important addition to the Monographs on Physiology edited for so many years by the late Ernest Starling. In that series he stated that it was intended to set out the progress of physiology in those chapters in which the forward movement was the most pronounced. Dr. Wiggers' book has been most successful in accomplishing this intent and purpose in so far as the knowledge of the pressure pulses is concerned. The illustrations are numerous and to the point. The very complete bibliography is of great value, twenty-seven of the papers included are by Wiggers himself, good evidence of his ability to deal authoritatively with the subject.

*Studies on Scurvy. Stanford University Publications. Medical Sciences. Volume*

*II, Number B. By ARTHUR W. MEYER AND LEWIS M. MCCORMICK. 108 pages, numerous illustrations. Stanford University Press, Stanford University, California, 1928. Price: paper \$1.50, cloth \$2.50.*

*The Symptomatology and Gross Morphology of Experimental Scurvy in the Guinea Pig, by ARTHUR W. MEYER, the Minute Morphology of Experimental Scurvy in the Guinea Pig, by ARTHUR W. MEYER, and Some Characteristics of the Blood of the Guinea Pig in Experimental Scurvy, by LEWIS M. MCCORMICK.*

This monograph consists of three parts. The Symptomatology and Gross Morphology of Experimental Scurvy in the Guinea Pig, by Arthur W. Meyer, the Minute Morphology of Experimental Scurvy in the Guinea Pig, by Arthur W. Meyer, and Some Characteristics of the Blood of the Guinea Pig in Experimental Scurvy by Lewis M. McCormick.

A so-called synthetic, basic diet was not used in these experiments because the original object was to ascertain, if possible, the causes for the appearance of peculiar phenomena in guinea pigs kept on ordinary feeds and used in experimental anatomy. Among these phenomena were marked nervous manifestations and permanent as well as temporary locomotor disabilities. Regarding these symptoms as indicating scurvy, the new observations upon the gross pathology of experimental scurvy as reported by Meyer are: The highly nervous condition of some of the animals; the recovery of health of young pigs after a condition of complete helplessness in the posterior half of the body; the occurrence of permanent locomotor disabilities; shortening of the roots of the teeth by absorption so that the molars can be depressed below the level of the gums; the occurrence of pronounced gastric distention of the stomach in some animals and peritoneal momic lesions in the lungs or other fatty change in the liver, adrenals and other organs; necrotic areas in both liver and adrenals; and degenerative changes and fibrosis of the costal cartilages and regions remote from the chest and

to consider some of the more significant procedures and principles involved in the experimental study of the infection. In the first instance it has brought together into one chapter a consideration of the fluids, secretions and excretions of the tuberculous body. Following this, it enters into an exposition of methods for the detection of the tubercle bacillus by staining, isolation and animal inoculation, and gives a description of this microorganism and compares it with other acid-fast bacteria, and deals with serological diagnosis and with diagnosis by the use of tuberculin. Secondly it devotes a number of chapters to some of the general factors concerned in the infection of animals and the study of experimental tuberculosis. The guiding principle of the author, as expressed in the preface, has been to cover the subject as concisely as is consistent with adequacy of presentation. Therefore, he has sought to present clearly in each of the various parts of the book only so many of the available technical procedures as appeared to him to be commensurate with the immediate subject at hand, always with an eye to the conservation of space and the prevention of too much duplication of essentially similar methods. Of the methods outlined, most have proved dependable through long application, but a few have been included which are new and virtually untried, because selection has occasionally been made on promise and rationale as well as on demonstrated worth. This plan has led to the omission of many methods, some of them of unquestioned value. It was the author's desire to write a book which would be useful to practising physicians, to public health officials and laboratory workers in general and to medical students. Part I deals with the General Consideration of the Body Fluids and Excreta in Tuberculosis. Part II treats of Bacteriologic Diagnosis, with Chapters on the demonstration of the tubercle bacillus by staining methods, by methods of concentration and isolation, and by the inoculation of animals and a discussion of the tubercle bacillus, its cultivation and the non-pathogenic acid-fast bacteria. Part III treats of Diagnosis by

Use of Tuberculin, with Chapters on tuberculin and its preparation, and the diagnostic application of tuberculin, Part IV treats of Serological Diagnosis with Chapters on the Tuberculo-Complement Fixation and other Serological tests, Part V treats of Methods of Value in Studies of Tuberculosis Experimentally Produced, with Chapters on the inoculation of animals with the tubercle bacillus, induced tuberculosis in animals, methods of studying induced tuberculosis in animals, and histologic technique, while the final chapter treats of the equipment for a tuberculosis laboratory, with bibliography and index. The author has performed a most useful service in bringing together the various laboratory procedures that are concerned with the diagnosis and treatment of tuberculosis, as well as those adapted to research work in tuberculosis. It appears on inspection to have achieved most acceptably the aim set forth in the author's preface. A good word may be said for the new publishing house of Charles C. Thomas in the general excellence of this production both as to printing and binding. It is a very neat job.

*The Pressure Pulses in the Cardiovascular System. Monograph on Physiology.* By CARL J. WIGGERS, M. D., Professor of Physiology in the School of Medicine of Western Reserve University, Cleveland, Ohio. 200 pages, with diagrams and illustrations. Longmans, Green and Co., London-New York-Toronto, 1928. Price, \$5.00.

The book is dedicated to Graham I. Lusk. Its object has been the analysis, in the briefest manner possible, of the present status of our knowledge concerning the pressure pulses in the cardiovascular system. Apparatus for making cardiodynamic studies, comparable in accuracy to physical instruments used for other types of physiological investigation has been available for a comparatively short time only. Its use under controlled experimental conditions demands a specialized technique, and the evaluation of records must be tempered by an insight gained only by years of service. Consequently this important method for measuring

gating the dynamics of the heart and circulation has not been extensively employed. It may be safely asserted that the number of investigators can be counted on the digits of two hands. It is, therefore, the author's hope that aside from its use as a reference medium and its value as a review of the subject, this little book may encourage others to enter this fascinating and precise field of investigation. Chapter I is concerned with the evolution of graphic methods for registering pressure pulses, Chapter II with the registration of pressure curves by micro-manometers, Chapter III with the configuration of pressure pulses in the cavities of the heart, Chapter IV with sequence of cardiodynamic events as established by pressure pulses from the auricles, ventricles and the aortae, Chapter V with the arterial pulse, Chapter VI with the venous pulse, Chapter VII with the consecutive phases of the cardiac cycle and the criteria for this precise determination, Chapter VIII and IX with the response of the heart to physiological variable, Chapter X with the intimate character of the ventricular contraction and Chapter XI with the pressure pulses under certain abnormal types of ventricular contraction. There follows a bibliography and an index. This little volume succeeds admirably in the presentation of the facts concerning the pressure pulses and in the evaluation of the experimental results. The book is an important addition to the Monographs on Physiology edited for so many years by the late Ernest Starling. In that series he stated that it was intended to set out the progress of physiology in those chapters in which the forward movement was the most pronounced. Dr Wiggers' book has been most successful in accomplishing this intent and purpose, in so far as the knowledge of the pressure pulses is concerned. The illustrations are numerous and to the point. The very complete bibliography is of great value. Twenty-seven of the papers included are by Wiggers himself, good evidence of his ability to deal authoritatively with the subject.

*Studies on Scurvy*. Stanford University Publications Medical Sciences Volume

II, Number 2. By ARTHUR W MEYER AND LEWIS M MCCORMICK. 108 pages, numerous illustrations. Stanford University Press, Stanford University, California, 1928. Price paper \$1.50, cloth \$2.50.

*The Symptomatology and Gross Morphology of Experimental Scurvy in the Guinea Pig*, by ARTHUR W MEYER, *the Minute Morphology of Experimental Scurvy in the Guinea Pig*, by ARTHUR W MEYER, and *Some Characteristics of the Blood of the Guinea Pig in Experimental Scurvy*, by LEWIS M MCCORMICK.

This monograph consists of three parts. The Symptomatology and Gross Morphology of Experimental Scurvy in the Guinea Pig, by Arthur W Meyer, the Minute Morphology of Experimental Scurvy in the Guinea Pig, by Arthur W Meyer, and Some Characteristics of the Blood of the Guinea Pig in Experimental Scurvy, by Lewis M McCormick.

A so-called synthetic, basic diet was not used in these experiments because the original object was to ascertain, if possible, the causes for the appearance of peculiar phenomena in guinea pigs kept on ordinary feeds and used in experimental anatomy. Among these phenomena were marked nervous manifestations and permanent, as well as temporary, locomotor disabilities. Regarding these symptoms as indicating scurvy, the new observations upon the gross pathology of experimental scurvy as reported by Meyer are. The highly nervous condition of some of the animals, the recovery of health of young pigs after a condition of complete helplessness in the posterior half of the body, the occurrence of permanent locomotor disabilities, shortening of the roots of the teeth by absorption so that the molars can be depressed below the level of the gums, the occurrence of pronounced gastric distention of the

junctions. Some subcutaneous and muscular hemorrhage was almost always present, while duodenal, cecal, vesical and paravesical hemorrhages were common. The minute morphology showed hemorrhages in all parts of the body except in the gums and joints. There was a marked fatty infiltration and degeneration of the liver, kidneys, adrenals, and even in the lungs and the peribronchial cartilages, the pancreas, skeletal muscles and the blood walls. Degenerative changes other than fatty, resulting in the complete loss of substance, were observed in the cartilages, bones, teeth, muscles, many of the glandular organs, as well as in the central, peripheral and sympathetic nervous systems. This widely distributed liquefaction of the cytoplasm and cell walls results in destruction of cartilage cells and of the cartilaginous matrix, at least in the costal cartilages, in the detachment of the periosteum and periodontia, in reduction in caliber of the bones, and in both the caliber and the length of the implanted portions of the teeth. It may effect not only the separation of ununited epiphyses and loosening of the teeth but the complete destruction of the parenchyma of some areas in the glandular and other organs, in desquamation of the mucosa and renal epithelium, and in complete disintegration

of the walls of blood vessels. In addition to the fatty and lytic changes, coagulative changes, such as extreme waxy degeneration in the muscles, were also noted in glandular and nervous tissues. The only proliferative changes noted occurred in the costal cartilages and concerned an increase in caliber at the region of the costochondral junctions and an invasion of connective tissue into areas of degeneration. Necrotic areas on the surface and in the substance of the liver were occasionally observed, but may be wholly unrelated to scurvy. Vacuolation was common to many organs, and fenestration up to a marked degree was observed, especially in muscle, bone marrow, the pulp of the teeth, and also in the cord and brain. Definite cytological changes occurred in the blood of guinea pigs in experimental scurvy. These changes became evident after ten days on the scorbutic diet. They consist of a decrease in red cells, hemoglobin and color index, and apparent decrease in fragility, a relative decrease in the number of lymphocytes, an absolute increase in the polymorphonuclears, and an increase in reticulated and nucleated red blood cells and leukocytes. The eosinophile, basophile, monocyte and transitional cell counts were not considered characteristic of scurvy.



# College News Notes

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## PROGRAM

### THIRTEENTH ANNUAL CLINICAL SESSION

#### BOSTON COMMITTEES

JAMES H MEANS, *General Chairman*

#### COMMITTEE ON ARRANGEMENTS

JAMES H MEANS

WILLIAM B BREED

HENRY A CHRISTIAN

RANDALL CLIFFORD

CHESTER M JONES

ELLIOTT P JOSLIN

ROGER I LEE

GEORGE R MINOT

JOHN H MUSSER

JOHN PHILLIPS

JOSEPH H PRATT

FRITZ B TALBOT

CONRAD WESSELHOEFF

FRANKLIN W WHITE

#### COMMITTEE ON HALL

FRANKLIN W WHITE

#### COMMITTEE ON CLINICS

HENRY A CHRISTIAN

CHESTER M JONES

ELLIOTT P JOSLIN

GEORGE R MINOT

JOSEPH H PRATT

CONRAD WESSELHOEFF

#### COMMITTEE ON ENTERTAINMENT

RANDALL CLIFFORD

WILLIAM B BREED

FRITZ B TALBOT

#### PRELIMINARY PROGRAM

#### ANNUAL CLINICAL SESSION

#### THE AMERICAN COLLEGE OF PHYSICIANS

APRIL 8-12, 1929

Monday, April 8, 1929

OPENING SESSION, 2 30 O'CLOCK

Hotel Statler Ballroom

1 Addresses of Welcome David I Edsall, Dean of Harvard Medical School  
Alexander S Begg, Dean of Boston University Medical School A Warren Sterns, Dean of Tufts College Medical School

John M Birnie, President of Massachusetts Medical Society Lincoln Davis, President of Suffolk District Medical Society

2 Reply to Addresses of Welcome Charles F Martin, President of The American College of Physicians

3 Tuberculosis A Collection of Papers  
Lawson Brown, Secretary, L. A. A.

4 (Title not yet announced) Lewellys F Barker, Baltimore

5 Juvenile Diabetes I M Rabinowitch, Montreal.

6 Glycosuria James E Paullin, Atlanta

7 Clinical Aspects of Paroxysmal Hypertension M C Pincoffs, Baltimore

EVENING SESSION, 8 00 O'CLOCK  
Hotel Statler Ballroom

*Symposium on Deficiency Diseases*

1 The Fundamental Nature of Deficiencies George R Minot, Boston

2 Pathology of Deficiencies S Burt Wolbach, Boston

3 Biochemistry and Physiology of Deficiencies George R Cowgill, New Haven

4 Pernicious Anemia Randolph West, New York

Tuesday, April 9, 1929

MORNING, 9 00 TO 12 00 O'CLOCK  
Hospital Clinics

AFTERNOON, 2 30 TO 5 00 O'CLOCK  
Hotel Statler Ballroom

1 Fatigue and Infection W L Holman, Toronto

2 Neoplasms J B Murphy, New York

3 Specific Dynamic Action of Protein, Fat and Carbohydrate in Altered States of Nutrition Edward H Mason, Montreal.

4 The Relation of Neisserian Infection to the Various Types of Arthritis O H Perry Pepper, Philadelphia

5 The Fallacy of Vaccine Therapy Charles C Bass, New Orleans

6 The Treatment of Angina Pectoris Harlow Brooks, New York

7 The Coronary Problem Arthur R Elliott, Chicago

8 Clinical Aspects of Trichiniasis Lewis A Conner, New York.

9 An Intensive Clinical Study of a Graphic Method of Recording Blood Pressure Louis F Bishop and Louis F Bishop, Jr., New York

EVENING SESSION, 8 00 O'CLOCK  
Hotel Statler Ballroom

1. Psychiatry in Relation to Medicine Austin F Riggs, Stockbridge, Mass

2 Syphilis of the Adrenals and Its Relationship to the So-called Idiopathic Addison's Disease Aldred S Warthin, Ann Arbor.

3 Lung Syphilis R I Rizer, Minneapolis

A smoker will follow this session

Wednesday, April 10, 1929

MORNING, 9 00 TO 12 00 O'CLOCK  
Hospital Clinics

AFTERNOON, 2 30 O'CLOCK  
Hotel Statler Ballroom

1 The Treatment of General Paresis Harry C Solomon, Boston

2 Psychiatry's Part in Preventive Medicine Arthur H Ruggles, Providence

3 The Need of Emotional Data in the Medical History John Favill, Chicago

4 Milder Forms of Coronary Obstruction James B Herrick, Chicago

5 The Failing Heart of Middle Life David Riesman, Philadelphia

6. Hypertension George C Hale, London, Ont

7 Undulant Fever in the United States. George Blumer, New Haven

8 (Title not yet announced) Robert A Cooke, New York

9 Tobacco Smoking and Gastric Symptoms Irving Gray, Brooklyn.

EVENING SESSION, 8 00 O'CLOCK  
Hotel Statler Ballroom

1 Serums and Vaccines in the Prevention and Treatment of Disease Ben White, Boston

2 Clinico-Roentgenological Conference M C Sosman and Associates, Boston

Thursday, April 11, 1929

MORNING, 9 00 TO 12 00 O'CLOCK  
Hospital Clinics

AFTERNOON, 2 30 O'CLOCK  
Hotel Statler Ballroom

1. The Treatment of Acute Aspiration Cecil K Drinker, Boston

2 The Significance of Abnormal Metabolic Features in the Management of Thyrotoxicosis Walter W Palmer, New York

3 Can or Will the Internist Practice Preventive Medicine? George H Bigelow, Boston

4 Factors in the Prognosis of High Blood Pressure W W Herrick, New York

5 The Carotid Sinus Reflex (Hering), Its Use in the Diagnosis and Treatment of Certain Cardiovascular Diseases C Saul Danzer, Brooklyn

6 Lead Poisoning from Snuff Raymond J Reitzel, Galveston

The General Business Meeting of The College will be held at 4 00 in the Hotel Statler Ballroom All Masters and Fellows should attend

#### EVENING, 7 00 O'CLOCK

Annual Banquet of The College  
To be followed by a Dance

Address George E Vincent, President  
of Rockefeller Foundation

Friday, April 12, 1929

MORNING, 9 00 TO 12 00 O'CLOCK  
Hospital Clinics

AFTERNOON, 2 30 O'CLOCK  
Hotel Statler Ballroom

1 Motion Picture Demonstrating Its Value in Teaching Electrocardiographic Interpretations of Cardiac Arrhythmias Joseph B Wolfe, Philadelphia

2 Dr William Dunlop and Pioneer Canadian Medicine J W Crane, London, Ont

3 Rheumatic Fever Homer F Swift, New York

4 (Title not yet announced) J C Meakins, Montreal

5 Results to Be Expected in Malignant Disease Treated by Radiotherapy George E Pfahler, Philadelphia

6 The Problem of the Nervous Patient Charles H Nielson, St Louis

7 Endogenous Obesity—A Misconception L H Newburgh and M W Johnston, Ann Arbor

#### EVENING SESSION, 8 00 O'CLOCK

Hotel Statler Ballroom  
Convocation Exercises

The General Profession is cordially invited No special admission tickets are required

1 Convocation Ceremony

2 President's Address Charles F Martin, Montreal

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### PRELIMINARY PROGRAM OF SPECIAL CLINICS AND DEMONSTRATIONS

This year the general session will be held in the afternoons and evenings while clinics and demonstrations will be held in the mornings from 9 00 to 12 00

Special Admission Cards required Clinic reservation forms and full directions will accompany the Final Program Reservations may be made by mail or duly at the Registration Bureau

Special clinics and demonstrations will be held as follows

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### BETH ISRAEL HOSPITAL

Program in charge of Herrman L Blumgart

## B

## BOSTON CITY HOSPITAL

1. (A guest will give a clinic at this time; the name will be announced later.)

2 The Progress of the Boston City Hospital. John J. Dowling, Superintendent.

3. Treatment of Pneumonia Demonstration of Cases. Edwin A Locke

4. Clinic of Unusual Cases Francis W Palfrey.

5 Pernicious Anemia Demonstration of Cases William B. Castle.

6 Treatment of Anemias Demonstration of Cases George R Minot

## WEDNESDAY, APRIL 10, 1929

1. (A guest will give a clinic at this time, the name will be announced later)

2 Gastro-Intestinal Cases. Franklin W White.

3 Cardiac Cases William H Robey

4 Nephritis Cases William R Ohler

5 The Surgical Treatment of Pulmonary Tuberculosis Demonstration of Cases Edward D Churchill

Hypertension and Arteriosclerosis Demonstration of Cases Soma Weiss

## THURSDAY, APRIL 11, 1929

1 Cardiac Cases Edward N. Libby and Thomas J. O'Brien

2 A Case Illustrating the Value of the Electrocardiogram James M Faulkner

3 Epilepsy William G. Lennox

4 Diseases of the Coronary Vessels Demonstration of Cases. Joseph T. Wearn.

5 Peptic Ulcer Demonstration of Cases. Maurice Fremont-Smith.

6 Neurological Cases Stanley Cobb

7. (A guest will give a clinic at this time, the name will be announced later)

## FRIDAY, APRIL 12, 1929

1 (A guest will give a clinic at this time, the name will be announced later)

2 Cases of Disease of the Hemopoietic System Ralph C Larrabee.

3 Lymphoblastoma Demonstration of Cases Henry Jackson, Jr

4 Tropical Diseases Demonstration of Cases George C Shattuck

5 Fluoroscopic Diagnosis in Chest Conditions Demonstration of Cases Harold W Dana

6 Carcinoma of the Head of the Pancreas Demonstration of Cases Irving J Walker

## C

BOSTON CITY HOSPITAL  
THORNDIKE MEMORIAL LABORATORY

## WEDNESDAY AND THURSDAY

APRIL 10 AND 11

BETWEEN 10 30 AND 12 30

Demonstration of Researches Concerning the Following Topics

Dr Castle and Associates

Dr Jackson and Associates

Dr Lawrence and Associates

Dr Lennox

Dr Minot and Associates

Dr Nye and Associates

Dr Wearn and Associates

Dr Weiss and Associates

Anemia

Malignant Tumors

The Physiology and Pathology of White Cells

Epilepsy

The Blood

Bacteriological Problems

The Capillaries

Vascular Problems

**BOSTON CITY HOSPITAL  
SOUTH DEPARTMENT**

Program in charge of Edwin H. Place

Ward visits on (1) diphtheria, (2) scarlet fever, (3) a few of the other minor groups such as chicken pox, mumps, measles and whooping cough

Amphitheater demonstration of cases of chronic laryngeal injury and other damages resulting from contagious diseases

E

**BOSTON DISPENSARY**

TUESDAY, APRIL 9, 1929

- |   |  |
|---|--|
| 1 Heart Disease David Davis             | 4 Chronic Pancreatic Disease Bert B Hershenson |
| 2 Essential Hypertonia David Ayman      | 5 Tuberculosis H. Louis Kramer                 |
| 3 Neurological Clinic A. Warren Stearns |  |

THURSDAY, APRIL 11, 1929

- |   |  |
|---|--|
| 4 Obesity Mark Falcon-Lesses                | 1 Neurosyphilis Arthur Beck  |
| 5 Gastro-Intestinal Clinic Percy B Davidson | 2 Neurasthenia Joseph H. Kaplan  |
|   | 3 Nephrosis Tobert W. Buck   |
|   | 4 Domiciliary Medicine in Clinical Teaching—Selected Case Osadore Olef |
|   | 5 Domiciliary Medicine in Clinical Teaching—Selected Case Charles Korb |
|   | 6 Diabetes James H. Townsend   |

WEDNESDAY, APRIL 10, 1929

- 1 Bronchiectasis William Dameshek
- 2 Psychalgia Joseph H. Pratt
- 3 Arthritis John D. Adams

F

**CHILDREN'S HOSPITAL**

Program in charge of Kenneth D. Blackfan

G

**HOMEOPATHIC HOSPITAL  
EVANS MEMORIAL CLINIC**

TUESDAY, APRIL 9, 1929

- 1 Sterility Clinic Special Emphasis to be Placed on the Constitutional Factors in Sterility S. R. Meaker and A. W. Rowe

WEDNESDAY, APRIL 10, 1929

*Endocrine Clinic*

- 1 Endocrine Diagnosis and Therapy Charles H. Lawrence
- 2 Endocrine Disorders Associated with Otosclerosis and the Meniere Syndrome D. W. Drury
- 3 Eye Findings in Endocrine Disorders W. D. Rowland
- 4 Cases Presenting Outward Evidence of Endocrine Disorders Found on Study not to have Endocrine Disturbance A. W. Rowe

- 5 Dementia Praecox L. G. Hoskins
- 6 The Follicular Hormone J. C. Janney
- 7 Discussion on Sugar Metabolism as Influenced by Insulin in Pituitary Disease H. Ulrich and A. W. Rowe

THURSDAY, APRIL 11, 1929

*General Medical Clinic*

- 1 Heart Clinic W. D. Red
- 2 Intestinal Migraine C. W. McClure
- 3 Neurology N. H. Gerrick
- 4 Lung Abscess, Diagnosis and Treatment L. R. Johnson

FRIDAY, APRIL 12, 1929

(Program to be announced later)

## H MASSACHUSETTS GENERAL HOSPITAL

1. Clinic by James E. Paullin, Atlanta
- 2 Thoracic Clinic Frederick T. Lord
- 3 Cases of Hypertension William B. Breed
- 4 Cardiac Clinic Howard B. Sprague
- 5 Endocrine Clinic Walter Bauer and Dwight L. Sisco

WEDNESDAY, APRIL 10, 1929

- 1 Clinic by Lewellys F. Barker, Baltimore
- 2 Demonstration of Medical Cases William B. Robbins
- 3 Pediatric Clinic Fritz B. Talbot and Harold L. Higgins
- 4 Clinico-pathological conference Richard C. Cabot and Tracy B. Mallory
- 5 Diabetic Clinic Roy R. Wheeler

THURSDAY, APRIL 11, 1929

- 1 Clinic by O. H. Perry Pepper, Philadelphia
- 2 Neurological Clinic James B. Ayer
- 3 Psychotherapy of Gastro-Intestinal Diseases William Herman
- 4 Gastro-Intestinal Clinic Chester M. Jones
- 5 Indications for Splenectomy Arlie V. Bock
- 6 Cases of Pernicious Anemia Wyman Richardson

FRIDAY, APRIL 12, 1929

- 1 Clinic by J. C. Meakins, Montreal
- 2 Demonstration of Cases Gerald Blake
- 3 Medical Clinic James H. Means
- 4 Demonstration of Cases. F. Dennette Adams
- 5 Anaphylaxis Clinic Francis M. Rackemann

## I NEW ENGLAND BAPTIST HOSPITAL

Program in charge of Albert A. Hornor

## J NEW ENGLAND DEACONESS HOSPITAL

Program in charge of Elliott P. Joslin

- |  |  |
|--|--|
| 1 Carcinoma of the Colon and Colitis from the Surgical Point of View Daniel F. Jones | 4 Pedigreed Diabetics Elliott P. Joslin    |
| 2 Gastro-Intestinal Cases Sara M. Jordan and Chester Kiefer                          | 5 Surgery in Diabetics L. S. McKittrick    |
| 3 Thyroid Cases Frank H. Lahey   | 6 The Pathology of Diabetes Shields Warren |

There will be further additions to this program including clinics by larynologists, ophthalmologists, gynecologists and roentgenologists

## K PETER BENT BRIGHAM HOSPITAL

- |  |  |
|--|--|
| 1 Diagnosis of Certain Forms of Heart Disease Lewis A. Conner, New York. | 4 Some Considerations on the Relation of Cardio-Renal System to Surgery of the Urinary Organs William S. Quinby. |
| 2 Chronic Myocardial Disease Henry A. Christian                          | 5 Bronchoscopy in Lung Disease. Lyman C. Richards  |
| 3 Results of Treatment of Duodenal Ulcer E. S. Emery                     |  |

WEDNESDAY, APRIL 10, 1929

- 1 Cardiac Disease, the Result of Infectious Processes James B Herrick, Chicago
- 2 Gallbladder Disease Channing Frothingham
- 3 Bronchial Asthma I Chandler Walker
- 4 Anemia William P Murphy
- 5 Thrombophlebitis John Homans

THURSDAY, APRIL 11, 1929

- 1 Mitral Stenosis David Riesman, Philadelphia
- 2 Signs of Persisting Infection in Acute Rheumatic Fever Clifford L Derick

- 3 Hemorrhagic Nephritis James P O'Hare
- 4 A Surgeon's Views of the Treatment of Peptic Ulcer David Cheever
- 5 Neurosurgical Conditions Harvey Cushing

FRIDAY, APRIL 12, 1929

- 1 Hypertension Charles F Martin, Montreal
- 2 Vascular Disease in Diabetes Mellitus Reginald Fitz
- 3 Treatment of Certain Types of Cardiac Arrhythmia Samuel A Levine
- 4 Treatment of Trifacial Neuralgia Gilbert Horrax
- 5 Diuretics Henry A Christian

L

## ROBERT BRECK BRIGHAM HOSPITAL

Program in charge of Louis M Spears  
Clinics on Arthritis

M

## UNITED STATES NAVAL HOSPITAL

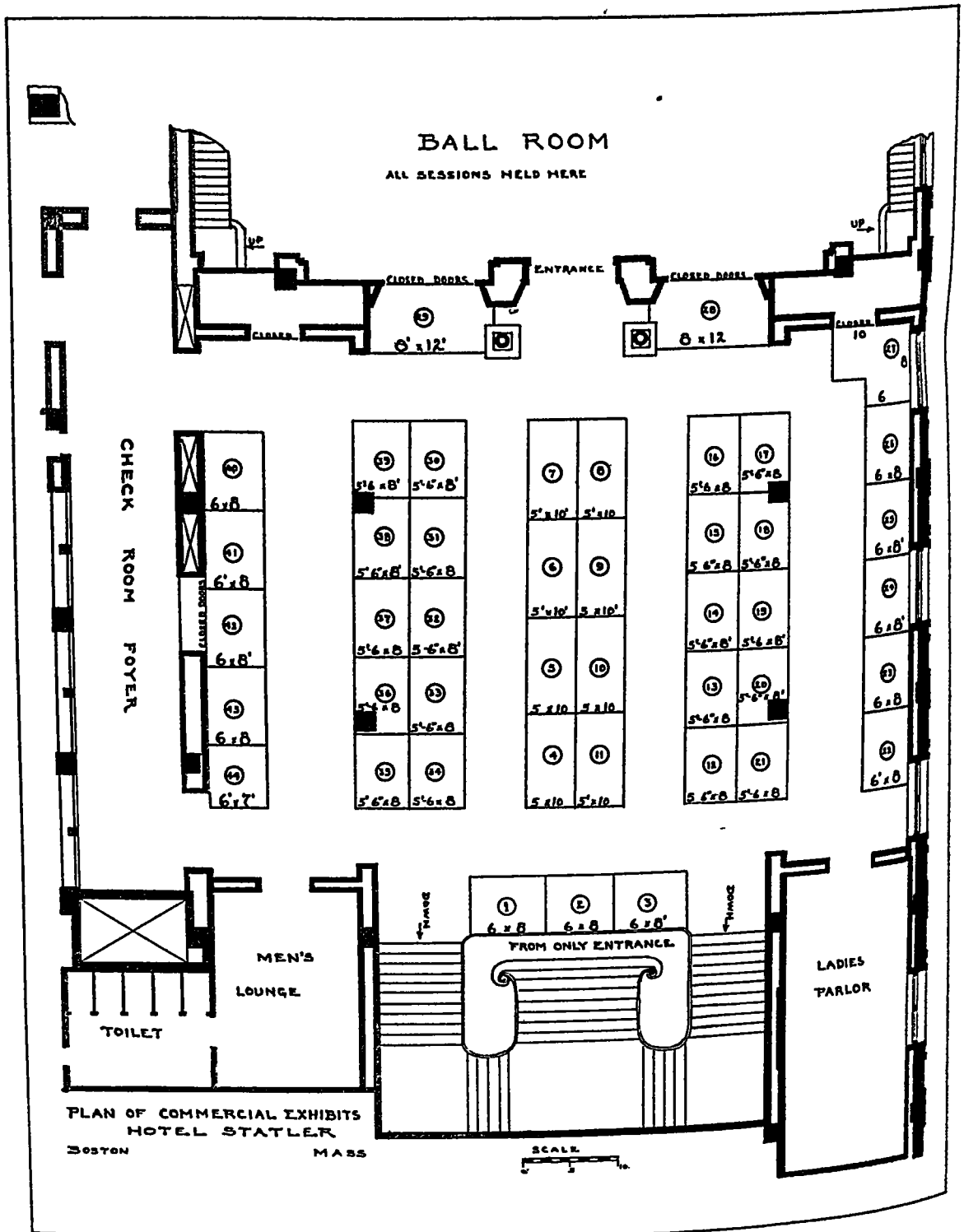
Program in charge of Capt F L Pleadwell, MC, U S N

Presentation of medical cases in the conference room of the hospital each morning Following this the group will be split up in sections of five Each section will be in charge of a ward medical officer, and the balance of the morning will be devoted to ward rounds

## TECHNICAL EXHIBIT

The technical exhibits have been arranged by the Executive Secretary, Mr E R Loveland, and the following chart shows the arrangement of booths and the assignment to exhibitors from various parts of the country The exhibits are highly diversified in their variety and will bring to the attendants at the Clinical Session, the latest and most improved equipment, the best pharmaceutical products, almost the whole library of medical publications and many other products of special interest to the Internist, Pediatrician, Neurologist, Psychiatrist, Radiologist and research worker

This Exhibit is undoubtedly the best arranged and the most popular one that The College has yet had The location is in the Ballroom Foyer where all attendants to the meeting will pass through the exhibits daily The Joseph T Griffin Decorating Company, of Louisville, Kentucky, who installed the exhibits for the American Medical Association, the Southern Medical Association and many other prominent medical societies, will be in charge of the booths and decorations





## LIST OF EXHIBITORS

SPACE	NAME	CITY AND STATE	PRODUCT
20	Abbott Laboratories	North Chicago, Ill	Pharmaceutical Products
12 & 21	D Appleton & Company	New York, N Y	Medical Publications
31	The Battle Creek Food Company	Battle Creek, Mich	Health Foods
22	Bausch & Lomb Optical Co	Rochester, N Y	Microscopes, Photomicro & Projection Apparatus
40	P Blakiston's Son & Co	Philadelphia, Pa	Medical Publications
13	The Borden Sales Company, Inc	New York, N Y	Merrell Soule Infant Foods
26	Britesun, Inc	Chicago, Ill	Therapeutic Lamps
25	Cambridge Instrument Co., Inc	New York, N Y	Electrocardiographs & Accessories, and other Physiological Instruments
3	Cameron's Surgical Specialty Co	Chicago, Ill	Electro-Diagnostic Surgical & Dental Instruments
44	G W Carnrick Co	Newark, N J	Pharmaceutical Products
1	Warren E Collins, Inc	Boston, Mass	Roth-Barach Oxygen Apparatus
14	F A Davis Company	Philadelphia, Pa	Medical Publications
16	Deshell Laboratories, Inc	Chicago, Ill	"Petrologar"
12 & 43	General X-Ray Company	Boston, Mass	"Morse" Wave Generator, GX-Galvane-Faradie Plate, Diathermy Apparatus, Electrodes
34	Paul B Hoeber, Inc	New York, N Y	Medical Publications
19	Horlick's Malted Milk Corporation	Racine, Wis	Malted Milk Products
17	Kalak Water Company, Inc	New York, N Y	Kalak Water
4	Charles B Knox Gelatine Co., Inc	Johnstown, N Y	Knox Gelatine
15	Lavoris Chemical Company	Minneapolis, Minn	"Lavoris"
15	LaMotte Chemical Products Co	Baltimore, Md	LaMotte Blood Chemistry Outfits
30	Lea & Febiger	Philadelphia, Pa	Medical Publications
9	J B Lippincott Company	Philadelphia, Pa	Medical Publications

27	MacGregor Instrument Company	Needham, Mass	Vim Stainless Steel Needles, Vim Emerald Luel Syringes, Vim Surgical & Medical Specialties Medical Publications
8	The Macmillan Company	New York, N Y	Anaesthetic Apparatus, Laboratory Equipment, Diagnostic & Scientific Apparatus, Vaccines, Intravenous Products, Orthopedic Appliances & Supplies, Instruments for Operating Room, E F M Catgut
2	E F. Mahady Company	Boston, Mass	Malpractice Insurance
18	The Medical Protective Company	Chicago, Ill	Mellin's Food
21	Mellin's Food Company	Boston, Mass	Pharmaceutical Products
38	Merck & Company, Inc.	Rahway, N J	Pharmaceutical Products
23	The Wm S Merrell Company	Cincinnati, Ohio	Infant Foods
32 & 37	Merrell Soule Company	New York, N Y	Medical Publications
35	The C V Mosby Company	St Louis, Mo	Medical Publications
39	Thomas Nelson & Sons	New York, N Y	Cod Liver Oil
28	The E L Patch Company	Boston, Mass	"Helioglass"
6	Pittsburgh Plate Glass Co	Pittsburgh, Pa	Psyllium Seed & Acidophilus Products
7	Richards, Inc	Glenolden, Pa	Medical Publications
11	W B Saunders Company	Philadelphia, Pa	"Graphic" Metabolism Apparatus
27	Sanborn Company	Cambridge, Mass	Optical Instruments, Projection Apparatus, Laboratory Equipment
11	Spencer Lens Company	Boston, Mass	Pollens, Ephedrine Preparations, Dextrose Ampoules and other Pharmaceutical Products
20	Swan-Myers Co	Indianapolis, Ind	Cod Liver Oil
16	Tailby-Nason Company	Boston, Mass	Electrocardiograph & Quartz Lamps
5 & 10	Victor X-Ray Corporation	Chicago, Ill	Pharmaceutical Products
11	{ Winthrop Chemical Company, Inc H A Metz Laboratories, Inc	New York, N. Y	

## THE MACMILLAN COMPANY

Booth 8

The Macmillan Company will display at Booth 8 a long list of recent and important medical books for the Internist. There are few other opportunities when one may leisurely look over the medical publications, past and recent, as at the Exhibit of this Clinical Session. Macmillan's announcements may also be found on page one of the Advertising Section of this journal.

## MERRELL SOULE COMPANY

Booths 32-37

Merrell-Soule Powdered Protein Milk is the dehydrated equivalent of Finkelstein's original Eiweissmilch and should not be confused with calcium caseinate or other preparations used in preparing a formula high in protein. The removal of a large proportion of the whey and retention of the lactic acid producing organisms in a viable condition contributes very largely to the product's therapeutic value. The wealth of clinical evidence accumulated in recent years compels us to submit that protein milk, as well as being ideal for, is the food of choice for the premature infant and for those types of nutritional disturbances characterized by hydrolability and inability to digest or assimilate normal formulae with consequent failure to gain. Samples and literature may be obtained by calling at the booths of the Merrell-Soule Company at the Exhibit during the Clinical Session.

## LEA &amp; FEBIGER

Booth 30

At Booth 30, Lea & Febiger will exhibit medical books of all descriptions, several by Fellows of The College. Orders may also be placed with them for subscription to the oldest medical journal in America devoted to Medicine, *The American Journal of Medical Sciences*. Lea & Febiger's announcements of publications may be found on page 8 of the Advertising Section of this journal.

## DASHELL LABORATORIES, INC

Booth 16

Petrolagar, the emulsion for use in place of plain mineral oil will be interestingly displayed at the meeting in Boston, April 8-12.

## KALAK WATER COMPANY

Booth 17

The Kalak Water Company will exhibit at Booth 17 "Kalak Water," made of distilled water and chemically pure salts of the kind normally present in the body. Kalak Water is non-laxative and higher in available alkali and richer in Calcium than any natural or artificial water known.

## D APPLETON &amp; COMPANY

Booths 12-21

A long list of important medical books and publications will be exhibited at the double booth of D Appleton & Company, where will be found a number of courteous men fully conversant with the field of medical publications to give you information and to show you the publications of this Company.

## THE BATTLE CREEK FOOD COMPANY

Booth 31

"Lacto-Dextrin," a special colon food for changing the intestinal flora to combat auto-intoxication, will be one of the products exhibited at Booth 31 by The Battle Creek Food Company. Their various pamphlets concerning all of their products will be gladly sent upon request.

## BAUSCH &amp; LOMB CO

Booth 22

Among the most important instruments which are universally used in the physician's laboratory throughout the world is the microscope. It has become a necessity for the study of bacteriology and pathology, for the making of bloodcounts and performing numerous other functions which make the medical practice what it is today.

Because of its fine resolution and high magnification, the Bausch & Lomb FFSA-8 Microscope is the instrument which enjoys the greatest popularity and has been chosen by the members of the medical profession as their laboratory instrument. This "Physicians' Microscope," as it is popularly designated, is an ideal instrument for bacteriological work. Its 43X (4mm) long working distance objective is unequalled for work with the haemocytometer.

The FFSA-8 is provided with a 10X and a 43X objective and a 97X oil immersion objective for high power work. These objectives together with the 5X and 10X huygenian eyepieces furnish a range from fifty to about one thousand times. Each of these objectives is mounted in standardized mounts, the lens elements being exactly set in threadless cells, so that precise centering of the lens element is assured.

The latest improvement of this Physicians' Microscope is the built-on mechanical stage which is indispensable in blood counting and offers a means for systematically examining a 50 by 75mm slide.

The FFSA-8 is regularly equipped with a divisible Abbe condenser, B & L Patented side fine adjustment and an improved rack and pinion substage.

This microscope is to be on exhibition at the meeting of The American College of Physicians in April, 1929. A detailed explanation and demonstration will be given at that time.

## THE WM S MERRELL COMPANY

Booth 23

Among products exhibited by The Wm S Merrell Company will be "Lacrimin," described as "milk of castor oil." This product is a thick creamy substance, perfectly emulsified, looking and tasting like whipped cream, but retaining the full effects of the castor oil, without its taste. Undoubtedly, such a product will find a warm welcome among physicians and patients other than children, for it happens all too often that a salt or pill is surreptitiously substituted for the castor oil prescription, even where the latter may be essential for correct results. Lacrimin can be prescribed without the patient being aware of the fact that he (or in the obstreperous case probably more often "she") is to take castor oil.

"It's Not the Cost—It's the Upkeep" is the title of an amusing little circular recently issued by The Wm S Merrell Company, depicting graphically the numerous "bribes" offered by fond parents to their unruly offspring refusing to take the "nasty castor oil" that the doctor prescribed.

## P BLAKISTON'S SON &amp; CO

Booth 40

P Blakiston's Son & Co, Publishers, Philadelphia, will exhibit in Space No 40 their publications on Medicine and Allied Sciences, including some English books and translations of some desirable foreign volumes. Special attention is directed to Kaufmann's "Pathology," 3 Volumes, translated by Reimann, Fulkerson "Text-book of Gynecology," Deaver's "Surgical Anatomy," 2nd Edition, Riehl & Von Zumbusch "Atlas of Diseases of the Skin", "Recent Advances Series", Smith "Forensic Medicine," 2nd Edition, Stitt "Tropical Diseases," 5th Edition, Halliburton "Physiology," 18th Edition, Gould's "New Medical Dictionary," 2nd Edition.

## LAMOTTE CHEMICAL PRODUCTS CO

Booth 45

LaMotte Blood Chemistry outfits offering simplified blood chemistry methods for the general practitioner as well as the technician will be displayed in a full line at Booth 45. Although the chart on a preceding page does not show this booth, so great has been the demand for exhibit spaces that additional booths have been arranged along the check room foyer, where the LaMotte Chemical Products Company has engaged a prominent location.

At the last annual session of the Southern Medical Association at Asheville, North Carolina, Dr Felix J Underwood (Fellow), State Health Officer for Mississippi, was elected Second Vice President, Dr William R Bathurst (Fellow), Little Rock, Ark, Chairman of the Board of Trustees, and Dr W S Leathers (Fellow), Nashville, Tenn, Dr Stewart R. Roberts (Fellow), Atlanta, Ga, and Dr Charles C Bass (Fellow), New Orleans, La, were elected members of the Board of Trustees

Dr V P Sydenstricker (Fellow), Augusta, Georgia, gave a medical clinic and Dr William A Mulherin (Fellow), Augusta, Georgia, gave a pediatric clinic before the Sixth District Medical Society at Macon, Georgia, on November 28

Dr William R Dancy (Fellow), Savannah, Georgia, is President-Elect of the Medical Association of Georgia, Dr Allen H Bunce (Fellow), Atlanta, is Secretary-Treasurer

Dr Morris H Kahn (Fellow), New York City, recently delivered a lecture before the Lackawanna County Medical Society in Scranton, Pa, on the subject "The Industrial Aspects of Heart Disease"

Dr John H Musser (Fellow and President-Elect), New Orleans, addressed the Issaquena-Sharkey-Warren Counties Medical Society at Vicksburg, Mississippi, December 11, on "Throat Infections in General Medicine"

Dr W McKim Marriott (Fellow and Third Vice President), St Louis, addressed the section on Pediatrics of the New York Academy of Medicine, January 3, on "The

Clinical Aspects of the Rôle of Focal Infections in producing Gastro-intestinal Symptoms in Infants and Children"

Dr Thomas Noxon Toomey (Fellow), St Louis, addressed the Lee (Iowa) County Medical Society at Fort Harrison, December 20, on "Pruritus and Dermatitis of Internal Origin"

Dr George B Eusterman (Fellow) Rochester, Minn, spoke before the Rice County (Minnesota) Medical Society at Northfield, November 26, on the subject "Appraisal of New Methods in the Diagnosis of Cholecystic Disease"

Dr John G Ryan (Fellow) of Denver, Colo, has recently become a Life Member through subscription to the Endowment Fund of The American College of Physicians

Dr H M Eberhard (Associate), Philadelphia, Professor of Gastro-Enterology at Hahnemann Medical College, recently described in detail "The Ionization of Zinc Sulphate in Chronic Colitis" in a clinic at the College

Dr George B Lake (Associate), Managing Editor of "Clinical Medicine and Surgery," North Chicago, Ill addressed the Lee County, Iowa, Medical Society, at Fort Madison, December 20, 1928 his subject being "Psychic Factors in Disease"

A small volume of Dr Lake's verses, "An Apostle of Joy," came out in December (Northshore Publishers, Highwood, Ill.), and articles of his appeared in the November "Welfare Magazine", November and December "Medical Economics" November and December "Hospital Topics" and "The

ci", and a verse in the November "Step Ladder" He was also reelected editor of *The Bulletin* of the Medical Round Table of Chicago at the annual meeting of that organization

Dr Cyrus W Strickler (Fellow), Atlanta, Ga, addressed the Fulton County Medical Society at Atlanta on December 6 on "Precordial Pain Simulating Angina Pectoris"

Dr Carl J Wiggers (Fellow), Cleveland, December 3, delivered the Chaile Memorial Oration before the Orleans Parish Medical Society at New Orleans

Dr Carl V Vischer (Fellow), Philadelphia, is author of an article in the January 1929 issue of *The Hahnemannian Monthly* entitled "The Management of the Chronic Tuberculous Patient"

Dr Charles W Stone (Fellow), Cleveland, addressed the Eighth District Medical Society at Nelsonville, Ohio, November 1, on "The Modern Trend" Dr Stone is president of the state medical society

Dr E Bates Block (Fellow), Atlanta, delivered an address on "Treat the Mind as Well as the Body" before the Kings County Medical Society, New York, on November 16

Dr Logan Clendenning (Fellow), Kansas City, at a meeting of the Jackson County (Mo) Medical Society commemorating the tercentenary of Dr William Harvey's publication of *De Motu Cordis*, November 27, spoke on "The Life and Labor of William Harvey"

Dr Max Emhorn (Fellow), New York, was one of the speakers at the inauguration of the lectures of the International Spanish Speaking Association of Physicians, Dentists and Pharmacists on November 27

Dr Charles W Burr (Fellow), Philadelphia, addressed the section on medical history of the Philadelphia College of Phy-

sicians, December 4, on "Dr Robert Whytt and Internal Hydrocephalus"

Dr James Marr Bisailon (Fellow), Portland, Oregon, addressed the Klickitat-Skamania Counties Medical Society, October 18, at White Salmon, Oregon, on "Mistakes in Diagnosis of Tuberculosis"

Dr Austin B Jones (Fellow), Kansas City, addressed the Clay County (Mo) Medical Society, October 25, on "Diagnosis and Treatment of Cardiac Disorders"

Dr James M Anders (Master), Philadelphia, November 24, spoke before the Association of College Presidents of Pennsylvania, Harrisburg, on "The Research Method of Teaching"

Dr Lawrence Selling (Fellow), Portland, Oregon, read a paper before the Central Willamette Medical Society in November, entitled "Changes in our Views of Neuroses"

Dr Oliver K Kimball (Fellow), Cleveland, addressed the Muskegon County Medical Society at its October meeting on "Prevention of Goiter Among School Children"

Dr William C Rucker (Fellow), New Orleans, was guest of honor at the annual banquet of the Orleans Parish Medical Society in December

Dr John Walker Moore (Fellow), Louisville, has assumed the duties of Dean of the School of Medicine of the University of Louisville, succeeding Dr Stuart Graves (Fellow), who has become Dean of the University of Alabama, School of Medicine, at Tuscaloosa

Dr Cyrus C Sturgis (Fellow), Ann Arbor, spoke before the Shiawassee County (Michigan) Medical Society at its November meeting on heart disease

Dr Sturgis also addressed the Milwaukee County Medical Society on November 9

Dr James L Bibb (Fellow), Chattanooga

nooga, has been elected President of the East Tennessee Medical Association for 1929

Dr Emanuel Libman (Fellow), New York, addressed the Kings County Medical Society, December 18, on "Some Phases of Rheumatic Fever"

Dr Frank Smithies (Fellow), Chicago, addressed the Marquette-Alger Counties Medical Society, November 3, on "Gastric Hemorrhage, Its Significance and Treatment"

Dr Gerald B Webb (Fellow), Colorado Springs, will address the medical section of the American Association for the Advancement of Science during its annual session on "The Rôle of Physicians as Poets and Men of Letters"

Rear Admiral Edward R Stitt (Fellow), Surgeon General of the United States Navy, retired voluntarily at the close of his second full term on November 30. Admiral Stitt was appointed Surgeon General by President Wilson on November 26, 1920, and was re-appointed by President Harding and President Coolidge. He has left Washington for duty as general inspector of activities of the Naval Medical Department on the Pacific Coast and in Hawaii

A bill has been introduced in the United States Senate by Senator Bruce to authorize Dr William S Thayer (Fellow), Baltimore, "to accept such decorations, orders and medals as have been tendered him by foreign governments." Government authority is necessary before members of the Medical Reserve Corps of the Army can accept foreign decorations

Dr Robert M Moore (Fellow), Indianapolis, addressed the November meeting of the Ft Wayne County Medical Society on heart disease

Dr Frederick Epplen (Fellow), Seattle conducted, on November 13, a pathological conference before the Walla Walla Valley

Medical Society. He presented specimens to illustrate obscure ulcerative and malignant conditions

Dr Arthur F Chace (Fellow), New York, was one of the speakers on January 9 at a testimonial dinner to Dr James McKernon at his retirement as President of the New York Postgraduate Medical School and Hospital

Dr Edward B Krumbhaar (Fellow), Philadelphia, was recently elected President of the Rush Society of the University of Pennsylvania

Dr Orlando H Petty (Fellow), Philadelphia, spoke before the Montgomery County (Pa.) Medical Society, November 7, on diabetes

Dr Warfield T Longcope (Fellow), Baltimore, Professor of Medicine at the Johns Hopkins Medical School, was one of the speakers at the dedicatory exercises, December 5, of the new dispensary and outpatient department of the Johns Hopkins University Medical School

Dr David Riesman (Fellow), Philadelphia, delivered an illustrated lecture on "Prehistoric Man" before the Brooklyn Institute of Arts and Sciences at the Academy of Music, January 5

Dr F M Pottenger (Fellow), Monrovia, Calif, presented a paper on "Disturbances in the Vegetative Nervous System in Diseases of the Lungs and Visceral Pleura" before the Association for Research in Nervous and Mental Disease, at its Ninth Annual Meeting, December 27-28, 1928, at the Hotel Commodore, New York City

Dr Edwin Henes, Jr (Fellow), Milwaukee, is engaged in editing and publishing the Atlanta 1928 Proceedings Volume of the Inter-State Post Graduate Medical Association of North America. This Volume will contain about one hundred articles (clinics and papers) contributed by about seventy of the leading physicians and sur-

geons of America and Europe. Most of the medical contributors, it is reported, are members of The American College of Physicians.

Dr V C Rowland (Fellow), Cleveland, has been elected Vice President of the Academy of Medicine of Cleveland. For a considerable period of time, Dr Rowland has been Editor of the Bulletin of the Academy, and Chairman of the Ohio State Medical Association Committee on Periodic Health Examinations.

Dr Estella G Norman (Fellow), Battle Creek, Michigan, on January 3 was reappointed as a member of the Michigan Board of Registration of Nurses and Trained Attendants by Fred W Green, Governor of the state.

Dr W S Leathers (Fellow), Dean, Vanderbilt University Medical School, Nashville, addressed a meeting at the Rutherford Hospital, Murfreesboro, December 6, on "The Hospital in Relation to the Community."

Dr J Gurney Taylor (Fellow), Milwaukee, was elected President of the Central States Pediatric Society at its recent annual meeting in Pittsburgh.

Secretary Wilbur nominated, on December 26, 1928, Capt Charles E Riggs as Surgeon General of the Navy and Chief of the Bureau of Medicine and Surgery to succeed Rear Admiral Edward R Stitt (Fellow), who has been transferred to the Pacific Coast to assume charge of the Navy's Medical activities there and in Hawaii. Capt Riggs has been in command of the Naval Hospital at Washington.

Dr E J G Beardsley (Fellow), Phila-

delphia, addressed the first Graduate Fortnight of the New York Academy of Medicine on "Practical Preventive Medicine."

#### GIFTS TO THE COLLEGE LIBRARY

Acknowledgment has been made of the following recent gifts to The College Library.

By Dr H M Pottenger (Fellow), Monrovia, Calif

Book, "Muscle Spasm and Degeneration"

Book, "Tuberculin in Diagnosis and Treatment"

Book, "Tuberculosis and How to Combat It"

Book, "Symptoms of Visceral Disease, 3d edition

Book, "Clinical Tuberculosis," Vol I, 2d edition

Book, "Clinical Tuberculosis," Vol II, 2d edition

By Dr Raymond J Reitzel (Associate), Galveston, Texas

Reprint, "Lobar Pneumonia in Negroes, The Influence of Syphilis as a Co-existing Disease"

Reprint, "The Effect of pH on the Oxygen Consumption of Tissues"

Reprint, "Parathyroid Extract—Collip as a Diuretic"

Reprint, "Liver Diet in the Treatment of Severe Anemia"

By Dr Philip B Matz (Fellow), U S Veterans Bureau, Washington, D C

Reprint, "Diseases of the Skin Among Ex-Service Men"

Reprint, "The Tuberculosis Problem in the United States Veterans Bureau"

All members are urged to donate copies of their own publications to the College Library, which is intended to be a memorial library and a directory of the publications of our Associates, Fellows and Masters.



## OBITUARY

*Dr Charles Launcelot Minor*

When Charles Launcelot Minor, M D, LL D, specialist in tuberculosis and brilliant writer, died at his home in Biltmore Forest, N C, in his sixty-fourth year Wednesday morning, December 26, 1928, the medical profession and The American College of Physicians lost a member who had achieved national and international fame

Although he had suffered from heart trouble for several years, his death came suddenly. He died at eight o'clock in the morning, a few minutes after he had begun to dress for breakfast

Dr Minor ranks with Trudeau in discovering and disseminating the treatment of tuberculosis. He was generally credited with having been the first physician to realize the importance of the psychological element in the management of tuberculous patients. He was a pioneer in perfecting the method of making physical examinations, which he early considered as important as laboratory tests

After securing his medical degree at the University of Virginia in 1888, Dr Minor was house physician in St Luke's Hospital in New York 1888-1890. He then went abroad, doing postgraduate work in Berlin, Dublin, London, Paris and Vienna. Returning to this country, he began the general practice of medicine in Washington, D C, but in 1895, having developed tuberculosis, he moved to Asheville which was thereafter his home

In studying his own case, he developed a deep interest in tuberculosis, and, having achieved a rapid recovery, began his career as a specialist in pulmonary diseases. His success was pronounced from the start. His reputation was soon established, and his fame became nation-wide

He was not satisfied with giving his patients the results of his study and genius. He had a veritable passion for educating both the public and the medical profession in the best way to combat what was then called "the Great White Plague"

He wrote on the subject constantly and forcefully. His contribution on "Symptoms and Diagnosis of Tuberculosis" in Klebs' "Tuberculosis," published by D Appleton and Company in 1908, still ranks as one of the greatest pronouncements on the subject in the English tongue

He contributed many articles to both medical and lay journals, all for the purpose of spreading the gospel of the effective treatment of tuberculosis. His brochures on the subject are regarded as classics in medical literature

Dr Minor was also in great demand as a speaker before medical conventions. His eloquence and his thorough knowledge of his subject, combined with his forceful personality, gave him a tremendous acquaintance and popularity among the physicians and surgeons of this and other countries

His eminence and success as a prac-

tioners were paid the tribute of many honors. He was president of the American Climatological and Clinical Association in 1916, president of the National Tuberculosis Association in 1918, president of the Southern Medical Association in 1924. He was a member of the American Medical Association, the Association of American Physicians, and of other medical societies. He was governor for North Carolina of the American College of Physicians.

His constructive ability in his profession was matched by his activities in the life of his home town. He was a member of the Pen and Plate Club, the Civitan Club and the Biltmore Forest Country Club, the Colonnade Club and the chapters of Delta Psi, Alpha Omega Alpha, and the Phi Beta Kappa fraternities at the University of Virginia.

He was a member and vestryman of Trinity Episcopal Church of Asheville. And with the same enthusiasm that he worked for the advancement of his church, he labored for the development and progress of his city.

No better description of Charles Launcelot Minor as a man can be found than the following paragraph from an editorial in "The Asheville Citizen" at the time of his death:

"But it is to his personality that his friends—and all Ashevilleans were his friends—today pay the proudest and most loving tribute. Dr. Minor was a man beloved by his community. His unfailing charm, his flashing wit, his profound and versatile scholarship, his lively interest in all human affairs and his eagerness to be of service to

whom he came in contact—

these qualities of the man endeared him to our people to a degree of affection that seldom is given to anybody."

In 1926, when Dr. Minor was given the degree of Doctor of Laws by the University of North Carolina, the citation accompanying the award, written by Dr. Archibald Henderson, said:

"Charles Launcelot Minor, Asheville. Born in Brooklyn, N. Y., M. D., of the University of Virginia, later prosecuted detailed researches in medical science in England and on the continent. Through intimate association with the famous Viennese bacteriologist Klebs, to whose renowned book 'Tuberculosis' he contributed an important chapter, he early turned the full current of his eclectic mentality upon the complex problems of tuberculosis, its diagnosis, treatment and prevention. Author of many authoritative scientific publications, chiefly devoted to the study of tuberculosis, he ranks today as an authority on that disease without a superior in the entire country. Versatile in attainments, eclectic in taste, like the late Dr. Weir Mitchell, he has, through the magic of his sympathetic and scintillating personality as well as by the depth of his knowledge and the range of his interests, won alike the unquestioned confidence and ardent devotion of his patients. Upon this scientific expert the University will now confer the degree of Doctor of Laws."

Funeral services for Dr. Minor were held the afternoon of December 27, 1928, at Trinity Episcopal Church in Asheville, with the Right Reverend Junius M. Horner, bishop of the dioc-

cese, and the Rev George Floyd Rogers rector of Trinity, officiating. The body was then taken to New York, where interment was made in Greenwood Cemetery.

Although he received the greater part of his education in Virginia schools and at the University of Virginia, and though he was so thoroughly identified with the South, Dr Minor was born in Brooklyn, N Y, May 10, 1865. His parents were Dr James Monroe Minor of Fredericksburg, Va, and Mrs Ellen J Pierrepont Minor of Brooklyn.

He is survived by his widow, who was Miss Mary McDowell Venable of Charlottesville, Va, and by three children, one of them a son, Dr John Minor, now practising medicine in Washington, D C.

Dr Minor was a great physician and a great citizen. He loved men and he loved books. His loyalty to friends and to his community and country was limitless. His career may well serve as a guide to any man who wishes to achieve eminence in his profession and worth to his fellows.

(Furnished by Dr Thompson Frazier (Fellow), Asheville, N C)

Dr Jacob Wolf (Fellow), Pittsburgh, Pa, died November 19, 1928, at Atlantic City, N J, of cerebral hemorrhage, aged 58.

Dr Wolf was born in Union City, Tenn, educated in Cincinnati where he also graduated from the Medical College of Ohio in 1891. He then spent some time in postgraduate work in Europe and in 1894 came to Pittsburgh where he located on the North Side eventually limiting his practice

to internal medicine. At the time of his death, he was the senior member of the medical staff of the Allegheny General Hospital of Pittsburgh. He had been a Fellow of the College since 1920.

(Furnished by D Lawrence Litchfield, Governor for Penn)

Dr Eric Kline Bartholomew (Fellow), Chicago, Ill, died December 18, 1929, of epidemic cerebrospinal meningitis contracted from a patient.

Dr Bartholomew received his medical degree from the University of Illinois, Chicago, in 1907. For several years he was assistant clinical professor of medicine at Loyola University School of Medicine, from 1914 to 1918 he was a member of the visiting staff of St Mary's of Nazareth Hospital, and later was a member of the senior medical staff of the same institution. At the time of his death he was also a member of the staff of the Lutheran Memorial Hospital. He was a member of the Chicago Medical Society, the Illinois State Medical Society and a Fellow of the American Medical Association. He was elected to Fellowship in The American College of Physicians April 3, 1922.

Dr Enoch H Miller (Fellow), Liberty, Mo, died October 8, 1928 of influenza and broncho-pneumonia.

Dr Miller was born in 1851, and received his medical degree from the Missouri Medical College, St Louis in 1874. He was a Fellow of the American Medical Association a member of his county and state medical societies, and had been a Fellow of The American College of Physicians since December 27, 1924.

## 1929 COLLEGE DUES

The Executive Secretary, Mr E R Loveland, 133-135 S Thirty-sixth Street, Philadelphia, Pa, distributed the bills for 1929 dues at the beginning of January. A great majority of the members have already mailed their checks and have received their 1929 Membership Cards. Several, however, have not to date paid the dues, and are urged to do so immediately. The 1929 Membership Card is necessary to register at the Boston Clinical Session in April, and none but those in good standing will be entered on the subscription list to receive Volume III of *Annals of Internal Medicine*, the new Year Book and other publications. It will assist the Executive Secretary greatly if all dues are paid promptly.

#### THE ADVERTISING SECTION OF THIS JOURNAL

Members and Subscribers have noted the addition and successful growth of Advertising in *Annals of Internal Medicine* during the past few months. In April, 1928, The Board of Regents authorized the Executive Secretary to start the promotion of advertising, and appointed an Advertising Censorship Committee consisting of

Dr. George Morris Piersol, Chairman

Dr Harlow Brooks

Dr E J G Beardsley

The Committee and the Executive Secretary have worked diligently to build up a high-grade advertising clientele, and seeks to enlist the assistance of every member and subscriber in further promoting this section. The Advertising Section of *Annals of Internal Medicine* is valuable to the College for it helps to defray a part of the cost of publication, it is valuable to the reader because it announces only high

grade products, apparatus and publications, and it must be lucrative to the advertiser to merit his continued patronage. It is known by the publishers that our members and subscribers do patronize our advertisers, but so frequently they do not mention the journal when placing orders or writing inquiries. To patronize our advertisers, to mention *Annals of Internal Medicine*, to recommend our advertising columns, are means of helping The College and of promoting the journal.

*Annals of Internal Medicine*, as the official journal of the American College of Physicians, has a *preferred circulation*, it arrives monthly at the offices of nearly two thousand eminent American internists, diagnosticians, pediatricians, psychiatrists, neurologists, radiologists, pathologists, bacteriologists, medical teachers and investigators, and tuberculosis and public health specialists. Its circulation is *national*, for it goes to every state and possession of the United States, it also goes to subscribers in Canada, Mexico and sixteen other foreign countries. *Annals* has attained, during its seven years of publication, an *eminence in American medicine*, excelled by no other journal devoted exclusively to Internal Medicine. The Advertising Section is limited to twenty pages in one issue, thus giving prominence for each advertisement, and therefore no advertisement is lost in a great host of other advertising. Furthermore, only high grade advertisements are accepted, each tendered advertisement passing review by the Censorship Committee.

Patronize our advertisers and use your influence with other organizations, whose advertising does not already appear in this journal, to adopt *Annals* as a medium for continuous advertising.

# Boston As A Medical Center

By HENRY A CHRISTIAN, M D

THE student of medicine who comes to Boston finds himself with access to modern, well equipped hospitals and medical laboratories. There is a wealth of clinical material, freely accessible to graduate and undergraduate medical students. Three excellent medical schools offer a large variety of medical courses. A splendid medical library hospitably invites the reader to use its fine collection of medical books.

In Boston, a city rich with traditions of able men and significant events, medicine, too, has its honored traditions. Here was established in 1782 one of the earliest American medical schools, from its inception an integral part of a university. In Boston in 1811 was founded the Massachusetts General Hospital one of our early hospitals, which since its opening in 1821 has never closed its doors to patients. At the Massachusetts General Hospital on October 16 1846 was performed that major surgical operation under ether anaesthesia, which more than anything else served to abolish pain from surgical procedures and made possible an ever increasing scope to surgical practice.

Founded in 1782 the Harvard Medical School occupied buildings of Harvard College in Cambridge until 1819 when it was moved to Boston

to secure better clinical opportunities for its students. In 1816, 1847, 1882, and 1906, respectively, special buildings were constructed in Boston for its use. In these a succession of eminent men have labored in the cause of medical education. The Warren family from the days of the battle of Bunker Hill has held a commanding position in Boston. Dr Joseph Warren played an important rôle in the Revolutionary War. His brother John Warren was Harvard's first professor of Anatomy and Surgery and since 1782, with but a brief interregnum, until last year, a Warren has held a professorial chair at Harvard. It was a Warren (John Collins Warren) who performed at the Massachusetts General Hospital that all significant operation under ether anaesthesia given at the hands of W T G Morton. Oliver Wendell Holmes essayist poet and professor of Anatomy gave the name anaesthesia to the process. Holmes' paper on puerperal fever was a very important step in bringing about a general acceptance of the contagiousness of that disease. Benjamin Waterhouse first professor of the Theory and Practice of Physic was a Leiden graduate and played an important rôle in the introduction into America of vaccination against small pox. In July 1800 he vaccinated first of all his

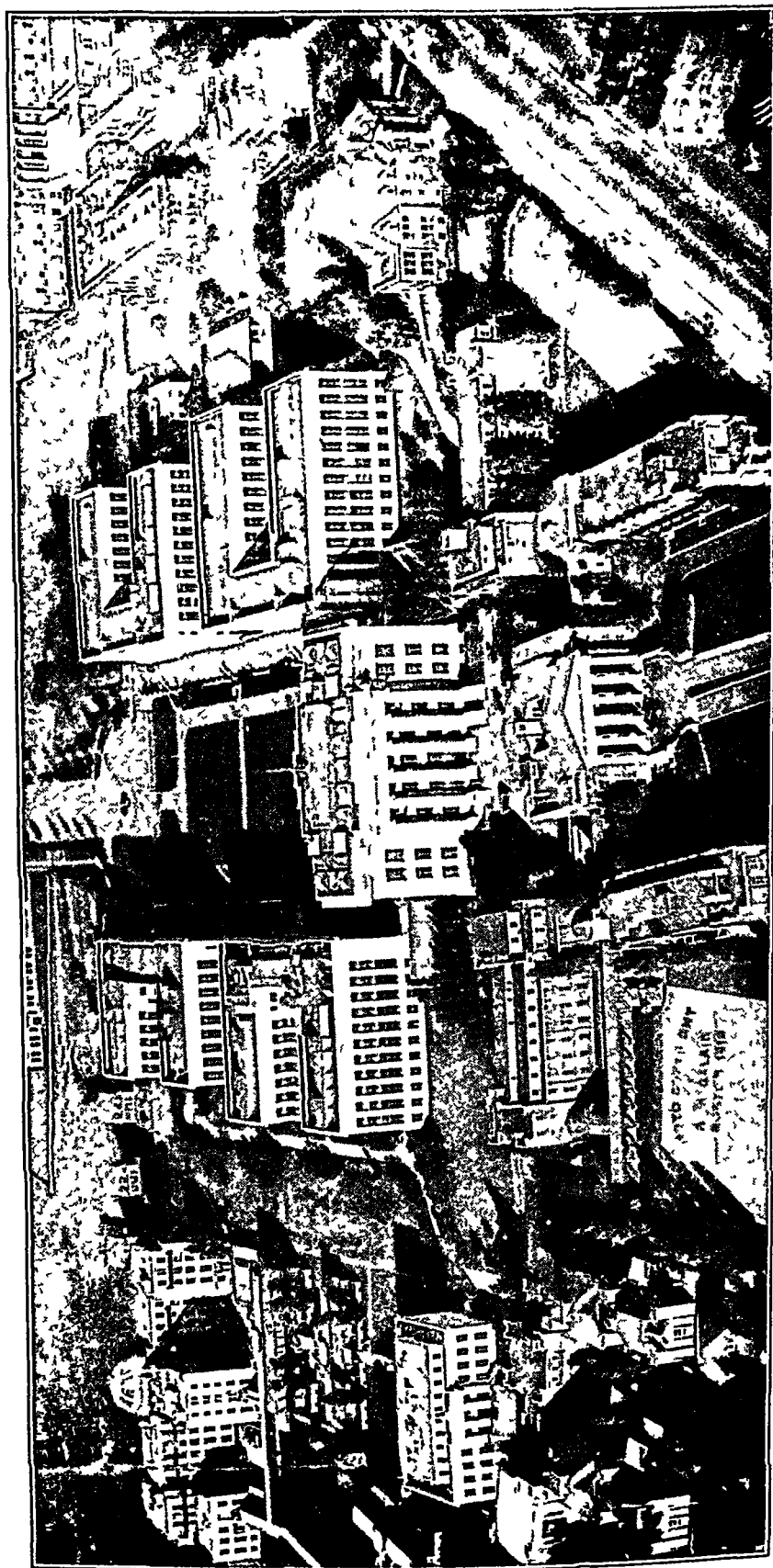


FIG 1 HARVARD MEDICAL SCHOOL, AIR-PLANE VIEW HARVARD MEDICAL SCHOOL, CENTER GROUP OF WHITE BUILDINGS IN FOREGROUND, PART OF PETER BLUNT BRIGHAM HOSPITAL AT LEFT, WHITE BUILDING IS HARVARD SCHOOL OF PUBLIC HEALTH BEYOND THIS ON LEFT ARE BUILDINGS OF CHILDREN'S HOSPITAL ON RIGHT IS HUNTINGTON MEMORIAL HOSPITAL AND HARVARD DENTAL SCHOOL

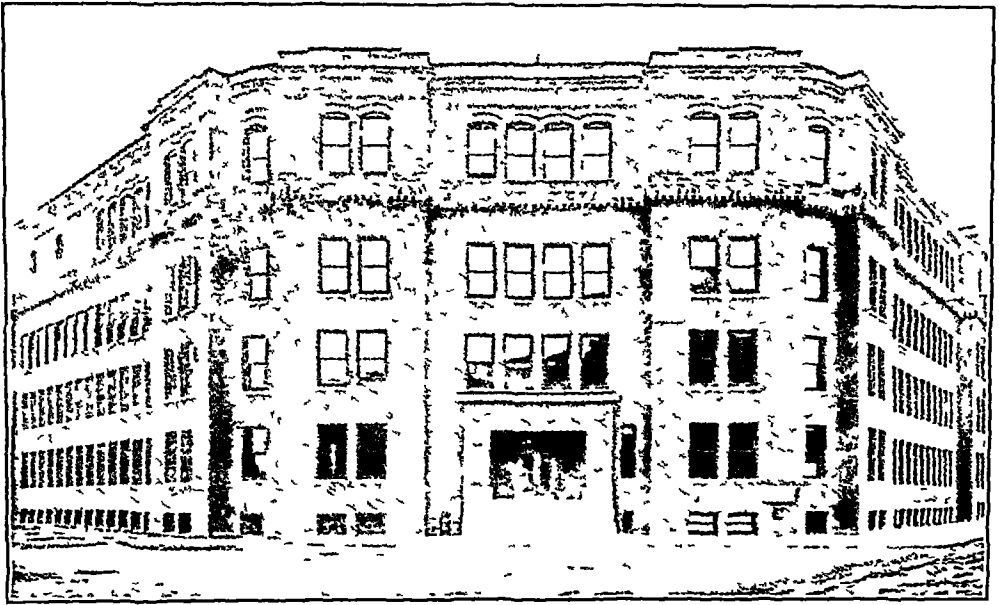


FIG 2 TUFTS COLLEGE MEDICAL SCHOOL

son and later others. At a subsequent date Dr. Waterhouse received from Jenner a silver snuff box containing vaccine inscribed "Edw. Jenner to B. Waterhouse." James Jackson with Warren was a founder of the Massachusetts General Hospital and a very outstanding medical man of his time whose "Letters to a Young Physician" are classic. Jacob Bigelow, Harvard's first professor of materia medica, recognized and taught the self-limitation of many infectious diseases. Henry J. Bigelow, a striking figure in surgery, described the Y-ligament and showed its importance in the reduction of dislocations of the hip. David W. Cheever, a remarkable lecturer, taught many students from his store of surgical wisdom. Henry P. Bowditch developed the first laboratory of physiology in this country and in it trained many of the men who subsequently organized departments of physiology in American medical schools. Theobald Smith, professor of Comparative Pathology, demonstrated insect trans-

mission of disease. Reginald Heber Fitz proved that the appendix is the most frequent point of origin of peritonitis and suggested the term "appendicitis," while a colleague, Maurice H. Richardson, spread the gospel of the importance of early operation in appendicitis. Fitz' work on pancreatitis also was of the pioneer type. A son, as Associate Professor of Medicine at Harvard, perpetuates his name in its medical associations. The Shattucks form another family group who have played an important rôle in Boston medicine. A Shattuck endowed the chair of pathological anatomy at Harvard in 1846; his son and grandson were professors in the departments of Medicine and wise practitioners of their time, teaching both the art and the science of medicine and a great grandson at present serves the school as assistant professor of Tropical Medicine. Richard C. Cabot, at the Massachusetts General Hospital, originated medical social service work. These and many others in the years

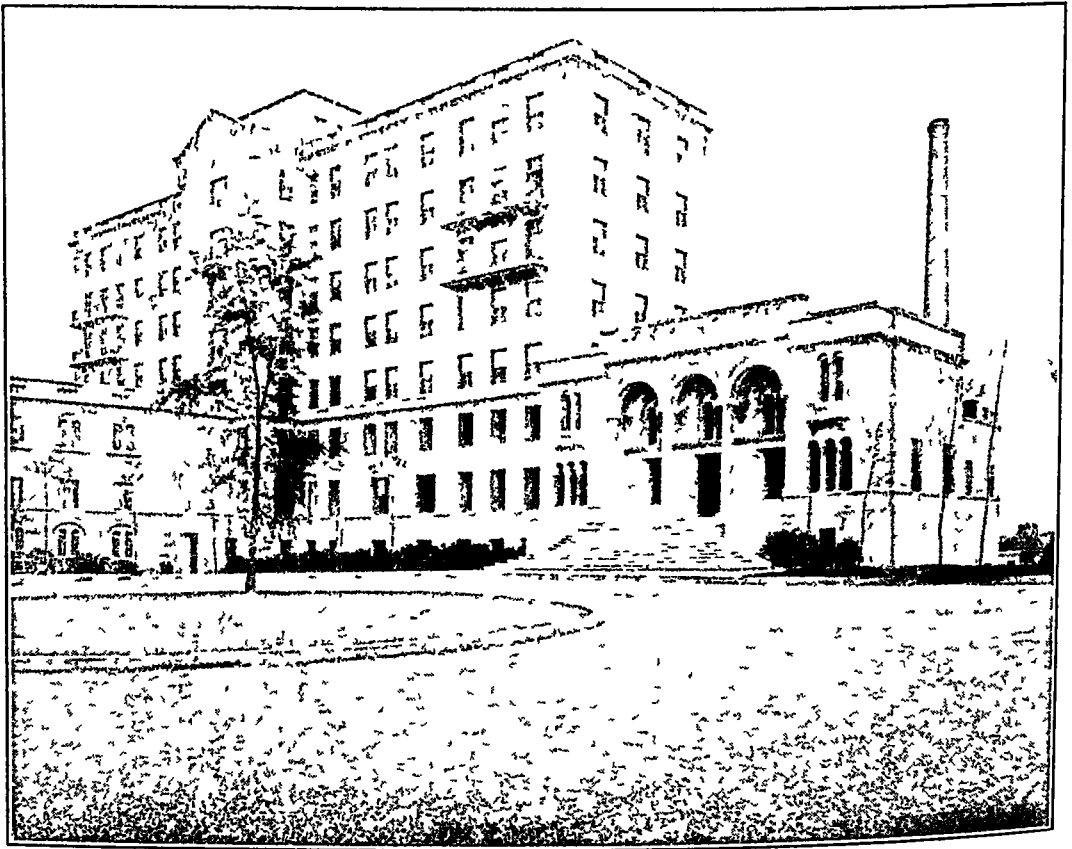


FIG 3 BETH ISRAEL HOSPITAL

since 1782, have built up for Boston truly an inspiring tradition of medicine

Three important medical schools are located in Boston, the Harvard Medical School, (Fig 1), founded in 1782, Boston University School of Medicine founded in 1873 and Tufts College Medical School founded in 1893. The first medical school for women in the United States was founded in Boston in 1848 as the New England Female Medical College. In 1873 this became the Medical Department of Boston University.

In 1927-28 there was an enrollment at Harvard of 521 candidates for the M.D. degree and 439 graduate students at Boston University of 205 candidates for the M.D. degree and at Tufts of 489 candidates for the M.D. degree. The Medical School

budget for the 1927-28 session was as follows, Harvard \$748,870.07, Boston University \$138,000.00, Tufts College \$149,095.18. In addition to the Medical School, Harvard has a school of Public Health with 26 enrolled students and a budget of \$214,309.19 in 1927-28. Both Boston University and Tufts College Medical Schools have building programmes which before many years will give to these institutions greatly improved facilities for medical instruction. The latter plans to move the work of the first two years to Medford where the collegiate department is and there to house the medical students in dormitories.

Boston possesses a large group of hospitals of first rank well equipped for the care of patients and possessed of laboratory facilities making possible



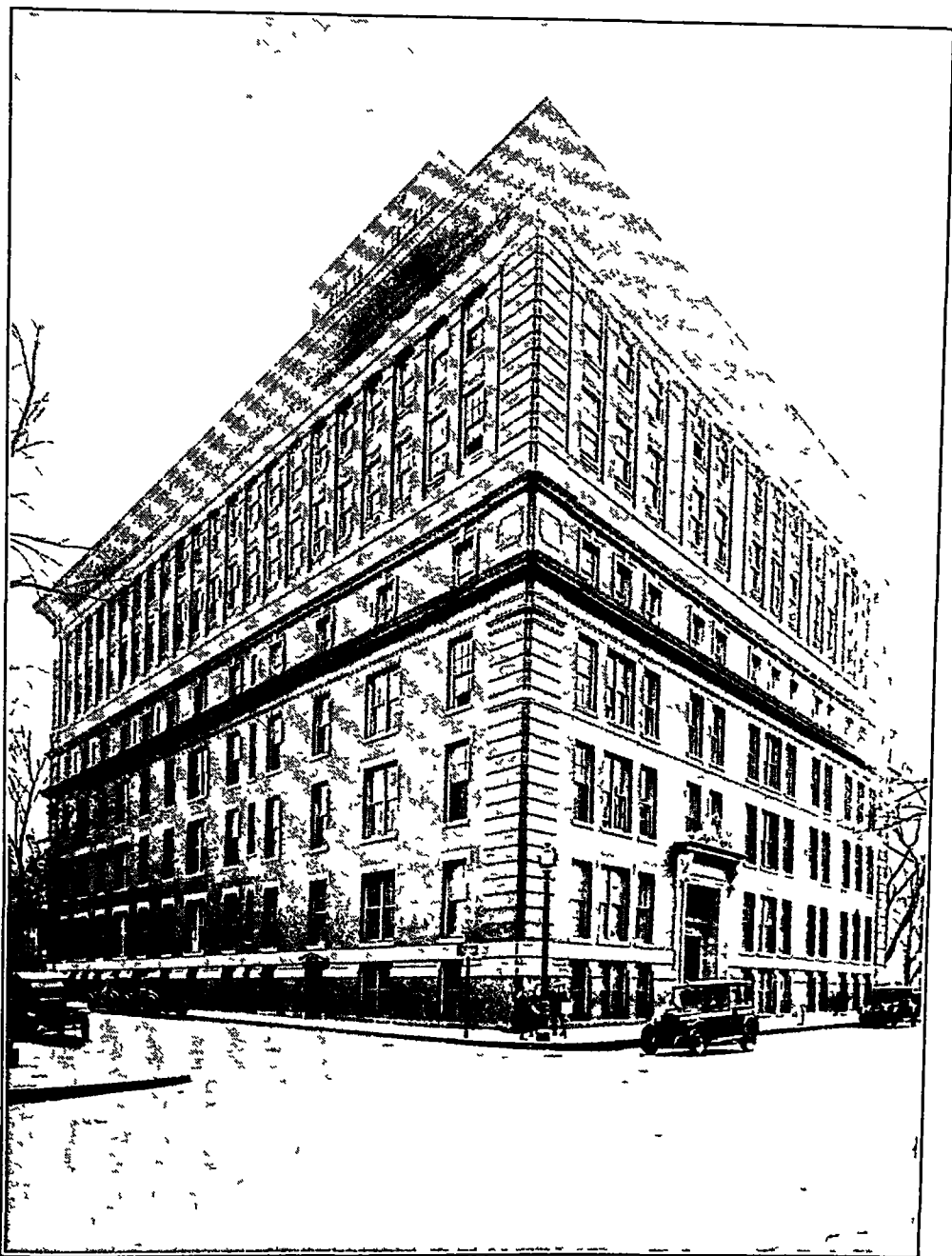


FIG. 4 BOSTON CITY HOSPITAL FRONT VIEW OF THE OUT-PATIENT DEPARTMENT

a wide range of medical investigations. In these hospitals the education of medical students, physicians, and nurses is being carried on throughout the year. These hospitals cooperate with the medical schools in such a generous way that in Boston

there has never been the need for university owned hospitals. This has brought about for the medical schools an enormous saving in expenditure for clinical facilities and allowed the medical schools to concentrate their resources on the budget for labora-

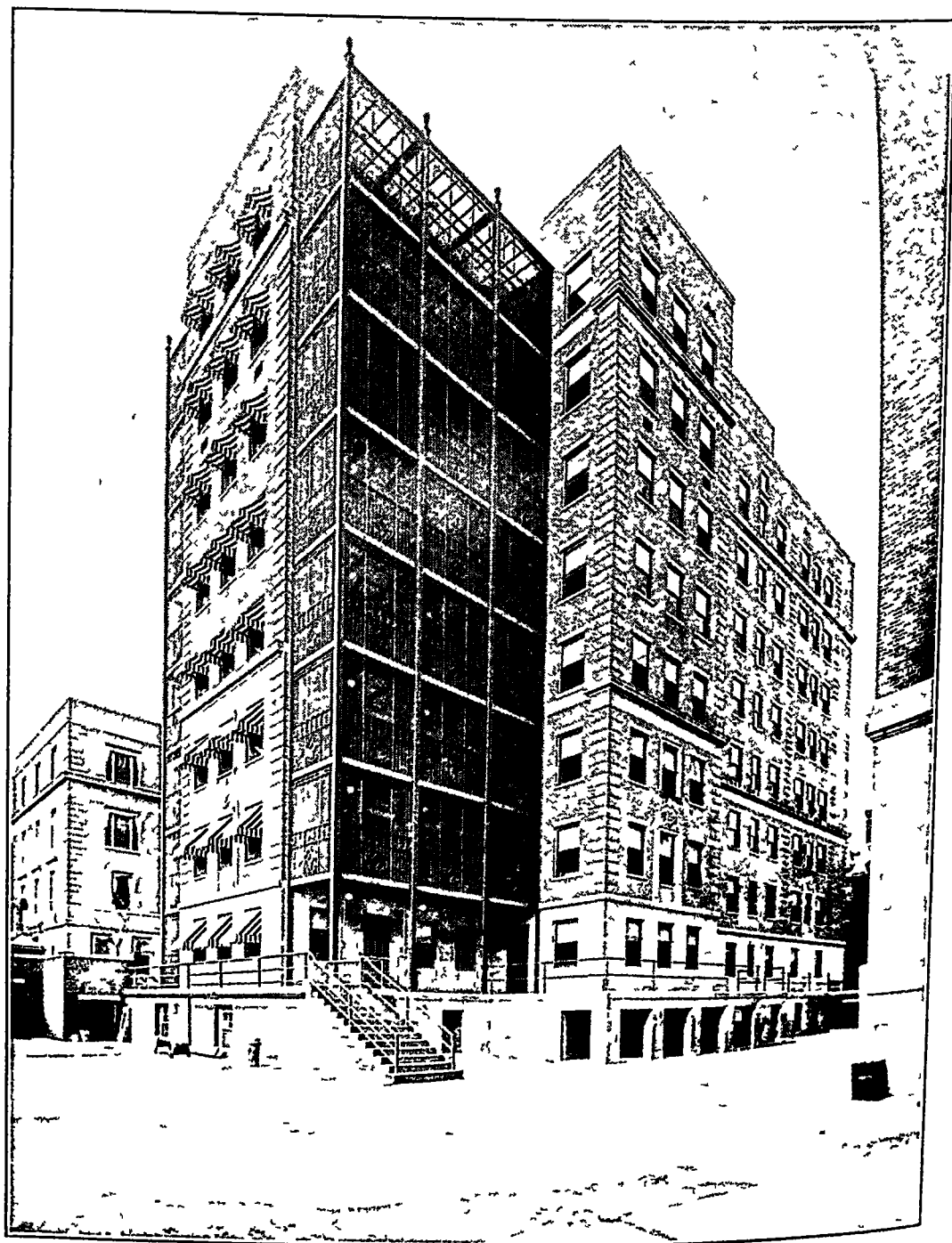


FIG 5 BOSTON CITY HOSPITAL. SIDE VIEW OF THE NEW SURGICAL BUILDING

tonies, instruction and investigation. Medical schools and hospitals have cooperated in making staff appointments so that the schools have freedom of selection of clinical teachers and the hospitals have profited by having added to their staffs men eminent in their branch of medicine.

freely selected from the country at large. Large clinical staffs in the various hospitals greatly reduces the burden of teaching put upon individual members of medical school departments. The spirit of whole hearted cooperation between hospitals and schools in Boston has been a great

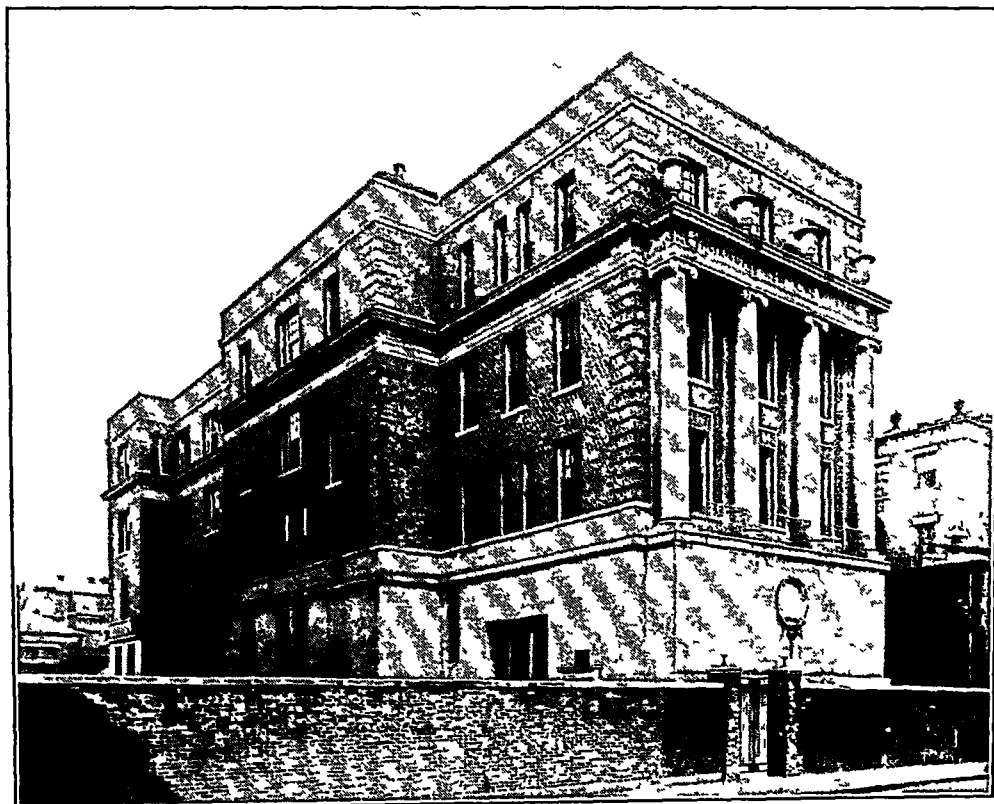


FIG 6 BOSTON CITY HOSPITAL FRONT VIEW OF THE THORNDIKE MEMORIAL LABORATORY

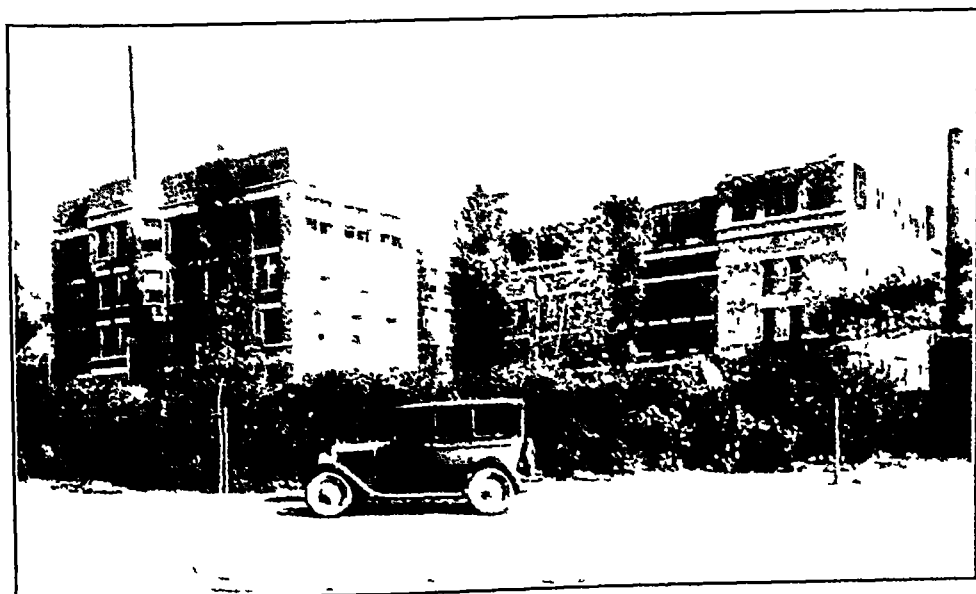


FIG 7 PSYCHOPATHIC HOSPITAL

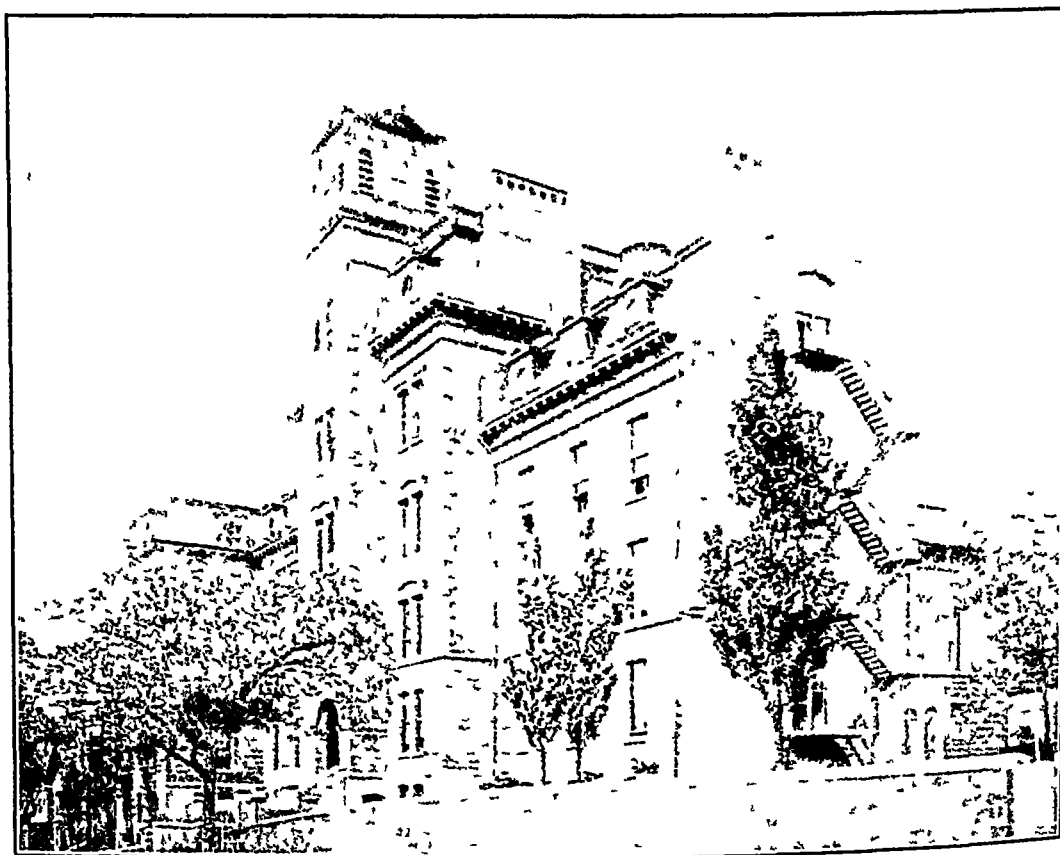


FIG 8 CARNEY HOSPITAL

factor in developing Boston into one of America's leading medical centers

The following brief statements about Boston's larger hospitals will serve to give some idea of the clinical facilities used here in medical teaching

Beth Israel Hospital, (Fig 3), recently constructed at a cost of \$3,000,000, has 180 beds. This is a general hospital with a variety of services

The Boston City Hospital, (Figs 4 and 5), is a general hospital with 1891 beds covering a variety of services. There is also a large Out-Patient Department where last year 81,728 new patients came for treatment. In connection with the hospital the Thonndike Memorial Laboratory, (Fig 6) furnishes extensive facilities for medical investigation. The South Department of the Boston City Hospital cares for contagious diseases and has

a capacity of 338 beds where last year 2,380 cases were treated. Under the Boston City Hospital's direction is a large hospital at Mattapan for the treatment of tuberculous patients with the capacity of 422 beds

The Boston Dispensary maintains a very large Out-Patient Department with 131,231 visits during the past year. In addition there is a well equipped hospital for children with 32 beds chiefly for medical cases

The Boston Lying-in Hospital has 100 beds and during last year treated 2089 patients of whom 1715 were delivered. In addition in the Out-Patient Department 1250 cases were attended

The Boston Psychopathic Hospital (Fig 7) is a state institution for acute, curable, incipient and doubtful cases of mental disease. It has 110

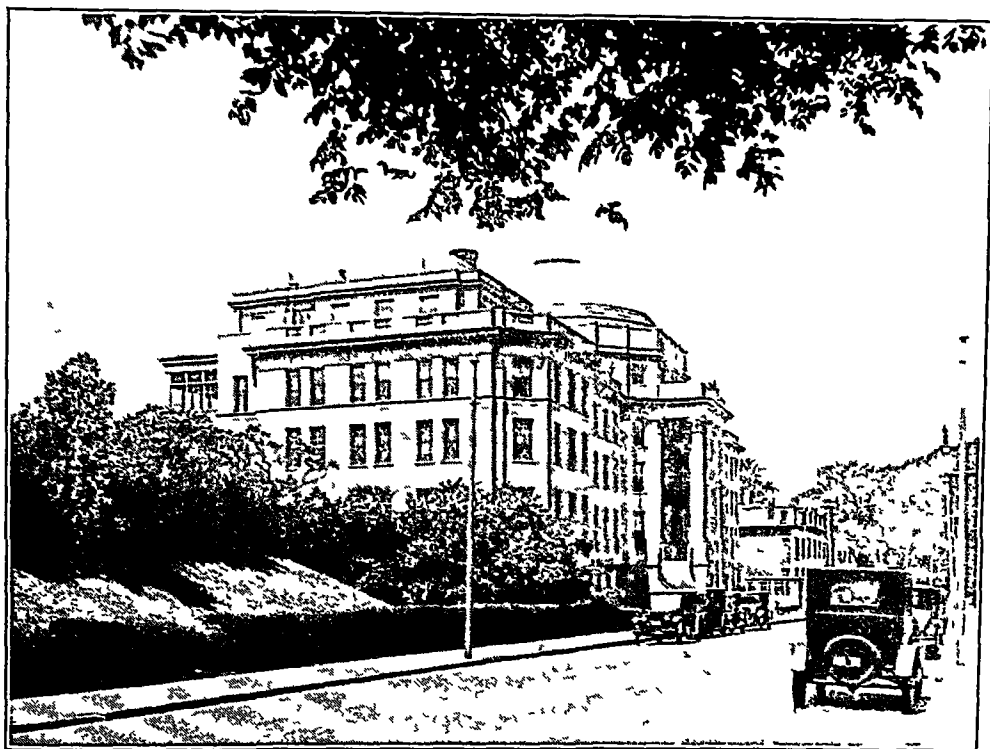


FIG 9 CHILDREN'S HOSPITAL ADMINISTRATION BUILDING



FIG 10 CHILDREN'S HOSPITAL, BIRD'S EYE VIEW



FIG 11 FREE HOSPITAL FOR WOMEN

beds and receives patients at the rate of about 1800 a year. There is also a large Out-Patient Department in connection with the hospital.

The Carney Hospital, (Fig 8), is a general hospital with 220 beds and a large Out-Patient Department.

The Children's Hospital, (Figs 9 and 10), has 244 beds where 5629 cases were treated last year. It has also a large Out-Patient Department in which 57,153 visits were made.

The Free Hospital for Women, (Fig 11), is devoted exclusively to the surgical treatment of diseases peculiar to women. It has a capacity of 94 beds and a large Out-Patient Department.

The House of the Good Samaritan is a chronic hospital for the care of women and children particularly those

with chronic heart disease and cancer. It has 75 beds.

The Infants' Hospital is adjacent to and under the management of the Children's Hospital. It has 66 beds for the care of infants.

Massachusetts Eye and Ear Infirmary, (Fig 12), has 290 beds for the care of patients with diseases of the eye and ear. There is also a large Out-Patient service where in 1927 there were 73,624 visits.

The Massachusetts General Hospital, (Fig 13), has 520 beds for general medical, surgical and pediatric cases, in addition there are special services for skin, orthopedics, laryngology, neurology, etc. Its large Out-Patient Department treated last year 31,871 new patients. The hospital also has extensive laboratories for special

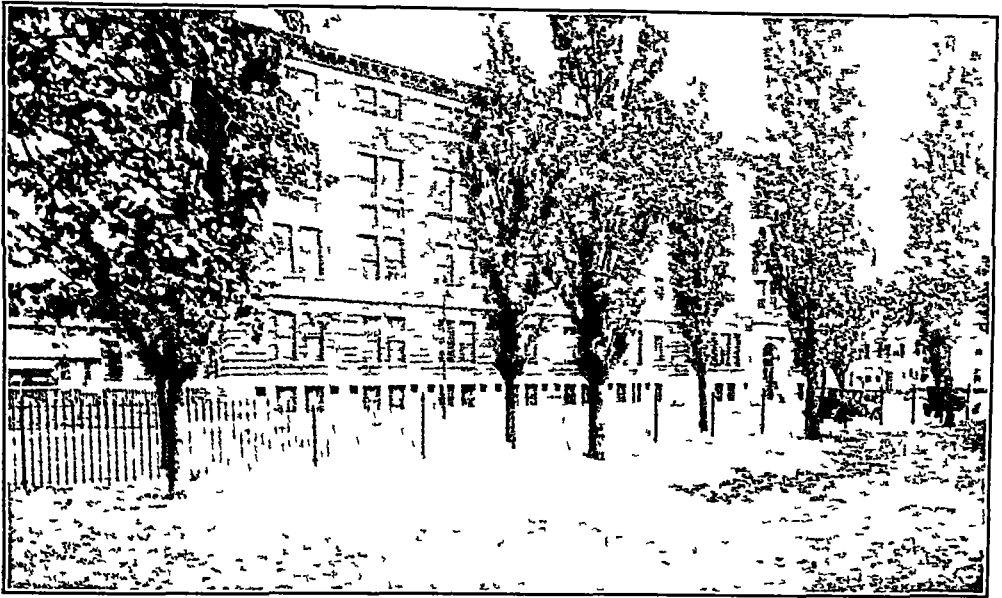


FIG 12 MASSACHUSETTS EYE AND EAR INFIRMARY



FIG 13 MASSACHUSETTS GENERAL HOSPITAL BULFINCH BUILDING IN THE FRONT OF WHICH THERE WAS USED IN MAJOR SURGERY ON OCTOBER 16 1846

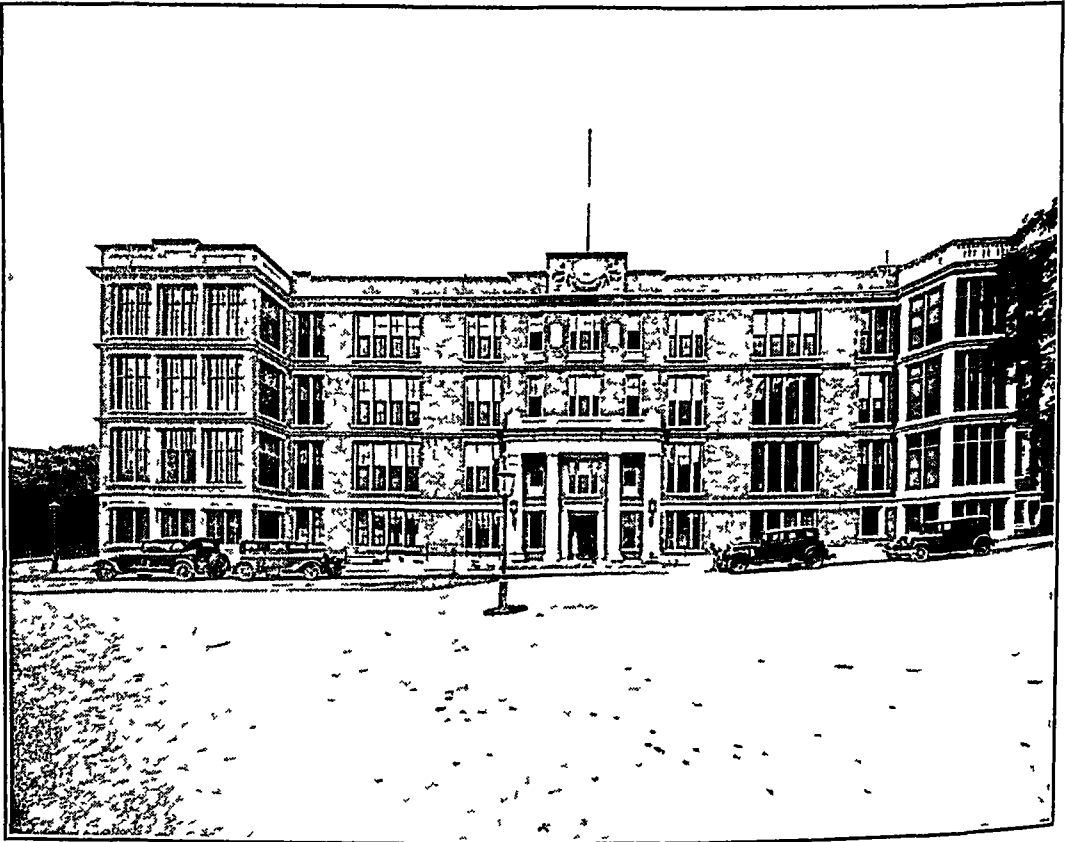


FIG 14 NEW ENGLAND DEACONESS HOSPITAL

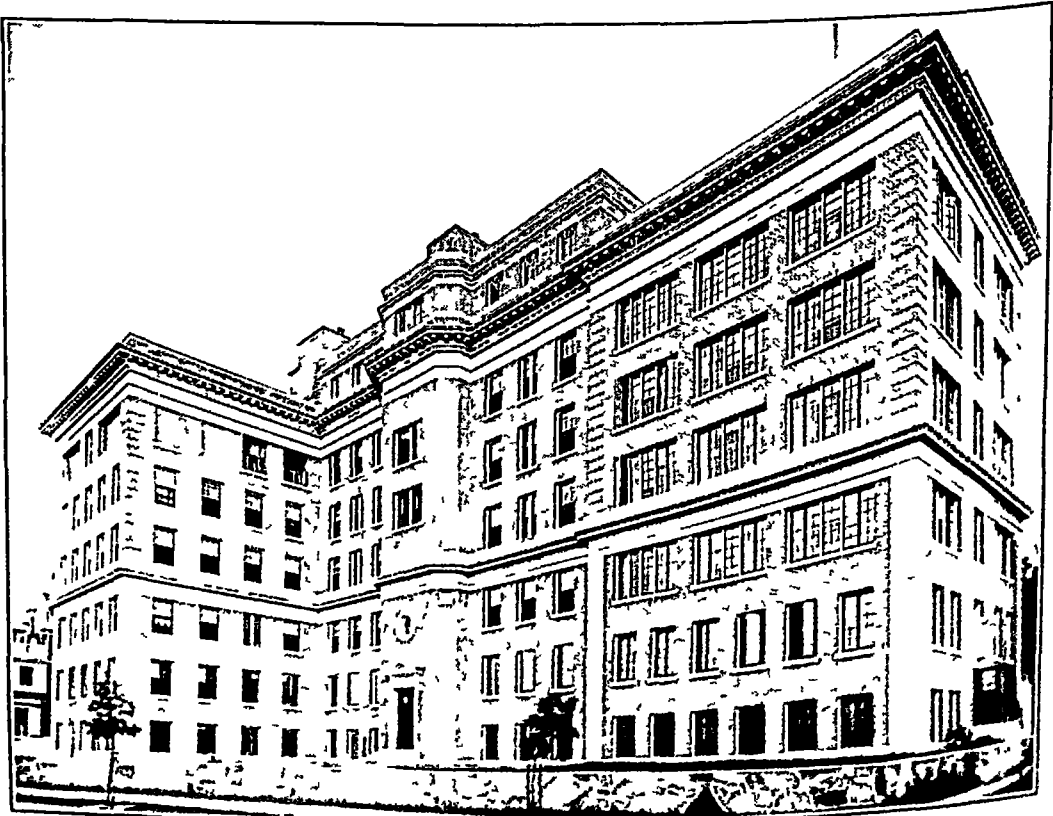


FIG 15 PALMER MEMORIAL HOSPITAL



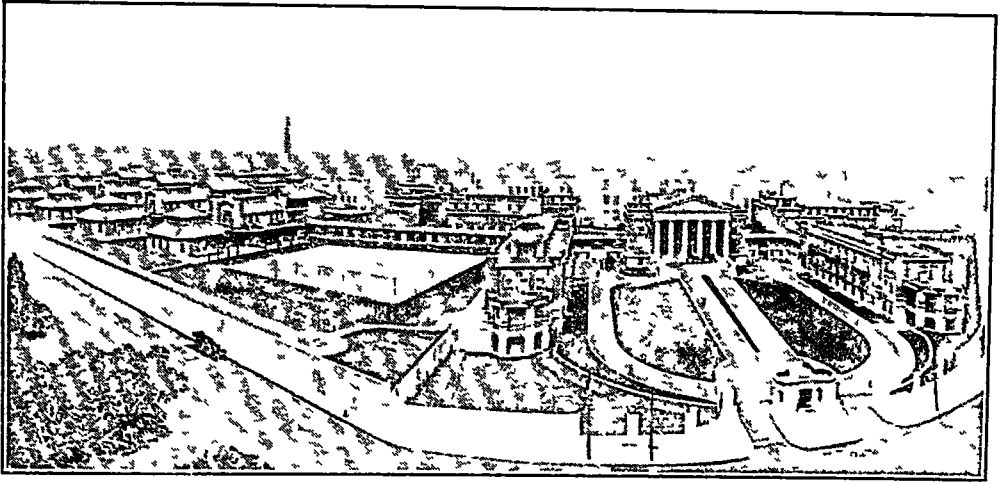


FIG 16 PETER BENT BRIGHAM HOSPITAL

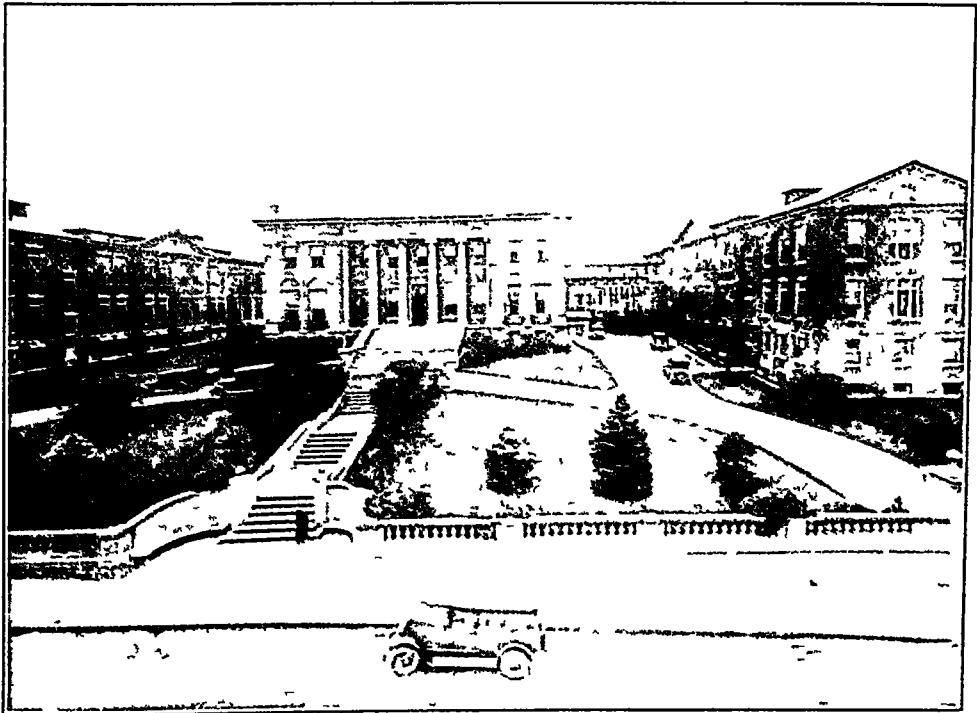


FIG 17 ROBT B. BRIGHAM HOSPITAL

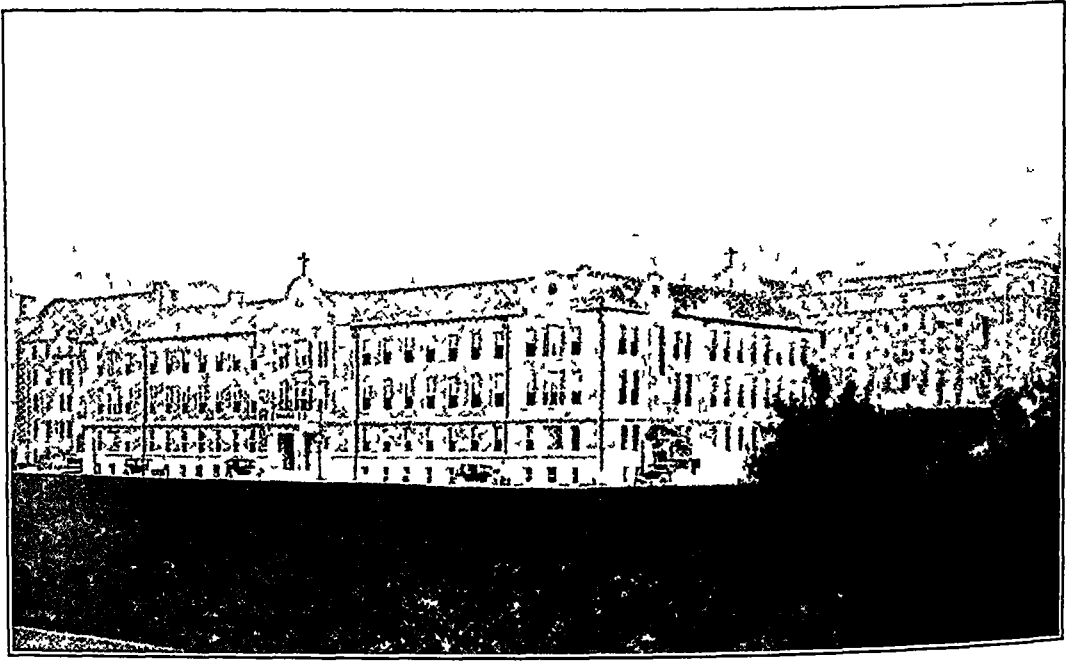


FIG 18 ST ELIZABETH'S HOSPITAL, BRIGHTON, MASS

investigation in addition to those for the routine study of hospital patients

The Massachusetts Homeopathic Hospital is a general hospital with Research, Maternity, Contagious and Out-Patient Departments. In addition, it maintains a small home, Sunnybank, for women convalescents, and assures the responsibility of supplying the Medical and Surgical staff for the Medical Mission Dispensary. It is the teaching hospital of Boston University School of Medicine. 530 beds, exclusive of those in its nurseries, are maintained. During 1927, 11,505 in-patients, of whom 1917 were maternity, were cared for and 57,980 visits were made to its Out-Patient Departments.

The New England Deaconess Hospital, (Fig 14), of 181 beds is devoted equally to medicine and surgery. Adjacent to it and under similar management is the Palmer Memorial

Hospital, (Fig 15), of 75 beds for chronic disease especially cancer. During 1927 there were 4,937 patients admitted to the two hospitals. The laboratories are highly developed, and are closely coordinated with those of the Harvard Cancer Commission.

The Peter Bent Brigham Hospital, (Fig 16), has 246 beds for general medical and surgical cases. It also maintains an Out-Door Department open all day long in which in 1927 there were 7699 new cases treated who made 60,671 visits. Besides laboratories for routine work there is extensive provision for medical investigation and laboratories in connection with hospital wards.

The Robert Breck Brigham Hospital, (Fig 17), has 110 beds for the treatment of patients with chronic disease.

St Elizabeth's Hospital (Fig 18), is a general hospital with 245 beds and a large Out-Patient Department.

# An Epidemic of Undulant Fever With a Study of the Associated Milk Supply

By MARIAN E. FARBAR, M.D., *College Physician, Richmond, Indiana*  
and

FRANK P. MATHEWS, D.V.M., *Department of Veterinary Science, Purdue University Agricultural Experiment Station, Lafayette, Indiana*

**B**Y no means a new though as yet, an unsolved problem faces us in the seemingly sudden endemic appearance of undulant fever in this country. It is with the hope of aiding in the solution of its epidemiology and in the meantime to encourage a preventive campaign which would include as one of its objectives the control of the source of the infection that the present outbreak is brought to the attention of the Medical Profession.

The patients and their milk supply were circumscribed on a college campus, hence a study of both the patients and the herd was possible. The first two cases appeared early in January 1928, and were diagnosed as "flu", the third with a longer run of fever was suspicious of typhoid fever, and a Widal was conducted but with negative results, the fourth was so typical of remittent malaria that Wright stains were made but no plasmodia were found. The fifth case suggested tularemia on account of the prolonged illness with a high fever, a history of rabbit contact, and acute conjunctivitis. Acting upon this suggestion, a specimen of blood was

sent to the Hygienic Laboratory, Washington, D. C., for a serological test, but a diagnosis of undulant fever was rendered by Dr. Edward Francis, whose timely assistance is hereby gratefully acknowledged.

A typical clinical syndrome of undulant fever was observed in twenty-five student patients and one laundress. A dizzy headache, malaise and nervousness marked the onset of the disease and preceded by several days other distressing symptoms such as chills, fever, and a sweating which was frequently profuse. A low pulse rate, 40 to 110, rarely above even with high fever was the rule. There was a mild leukopenia and an anemia present. All but four cases had two or more attacks of fever with apyrexia at intervals ranging from five days to two months. With the exception of these common symptoms the usual wide variety of clinical manifestations which have been observed in other outbreaks were noted. The accompanying fever charts illustrate the several types of the disease which were encountered.

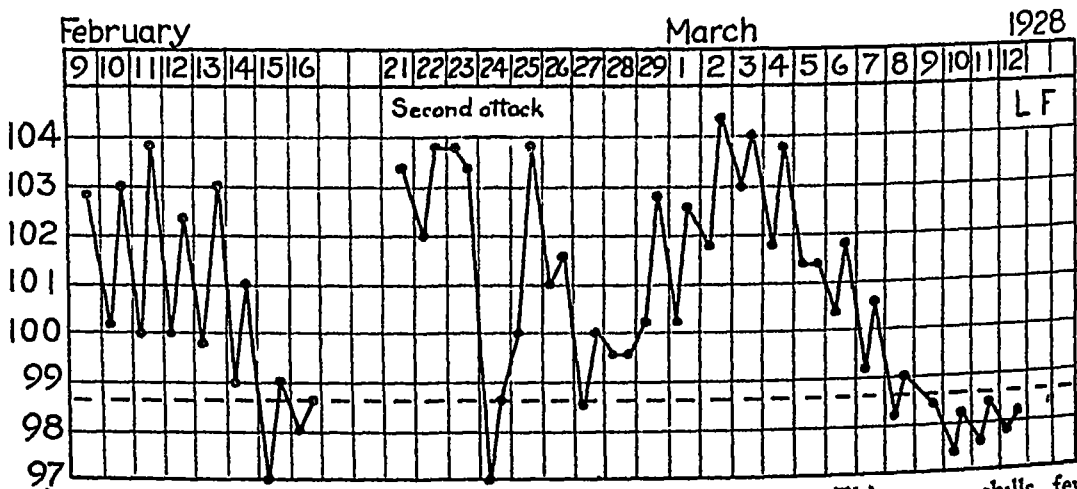


FIG 1—Chart L F From Pennsylvania, a football player This was a chills, fever and sweating case with no outstanding symptoms otherwise He is now apparently well and back on the squad

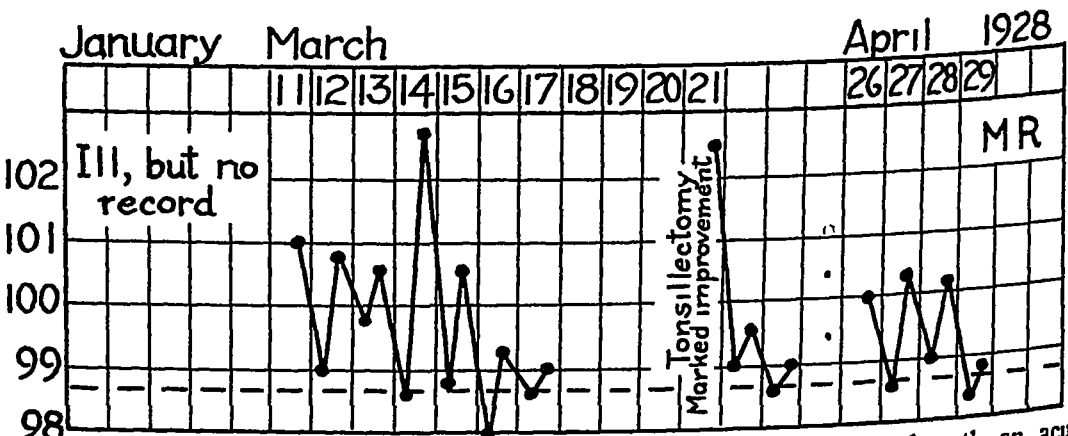


FIG 2—Chart M R From Virginia A severe case, complicated with an acute exacerbation of a chronic tonsilitis, improved rapidly after tonsillectomy

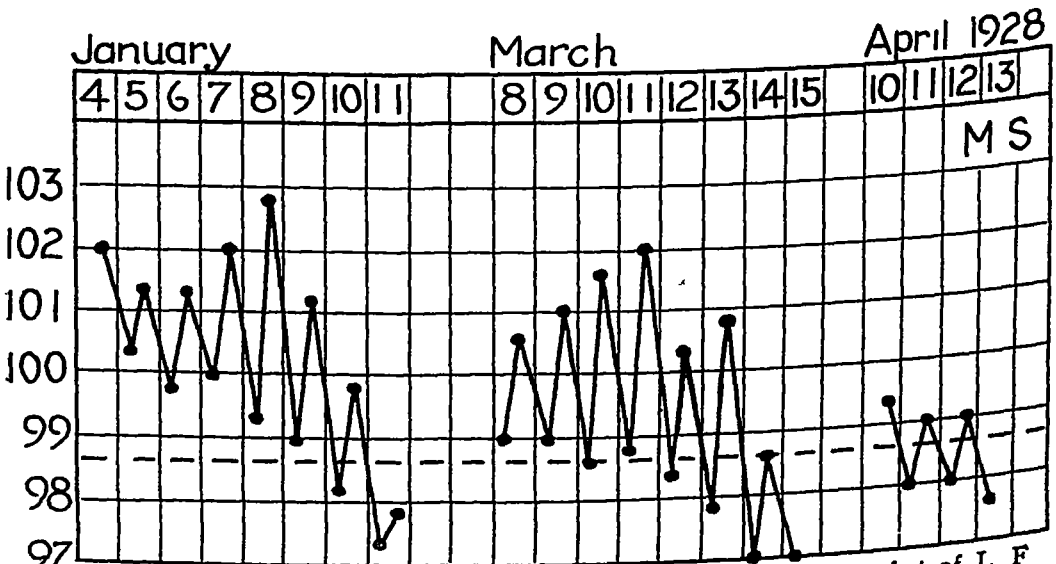


FIG 3—Chart M S From New York State A case similar to that of L F

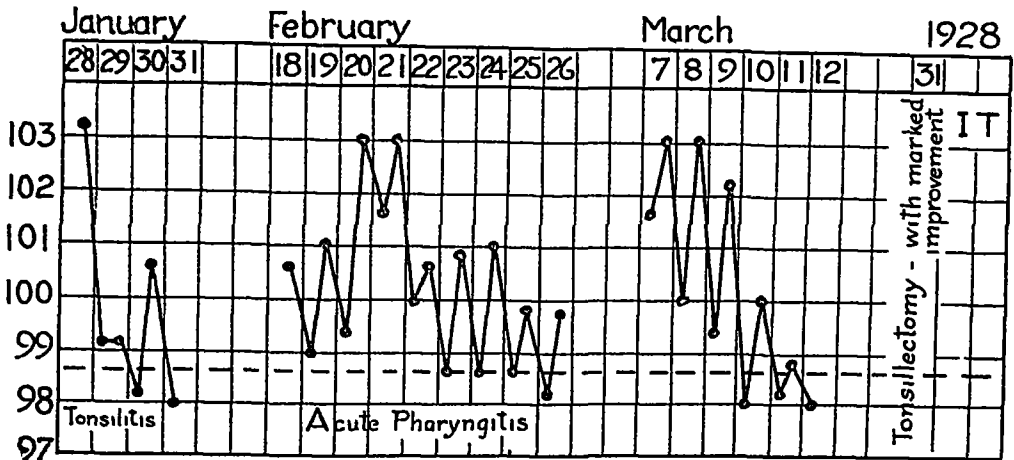


FIG 4—Chart I T A Japanese A case similar to that of M R These and several similar cases suggest chronic infected tonsils as a factor in predisposing etiology

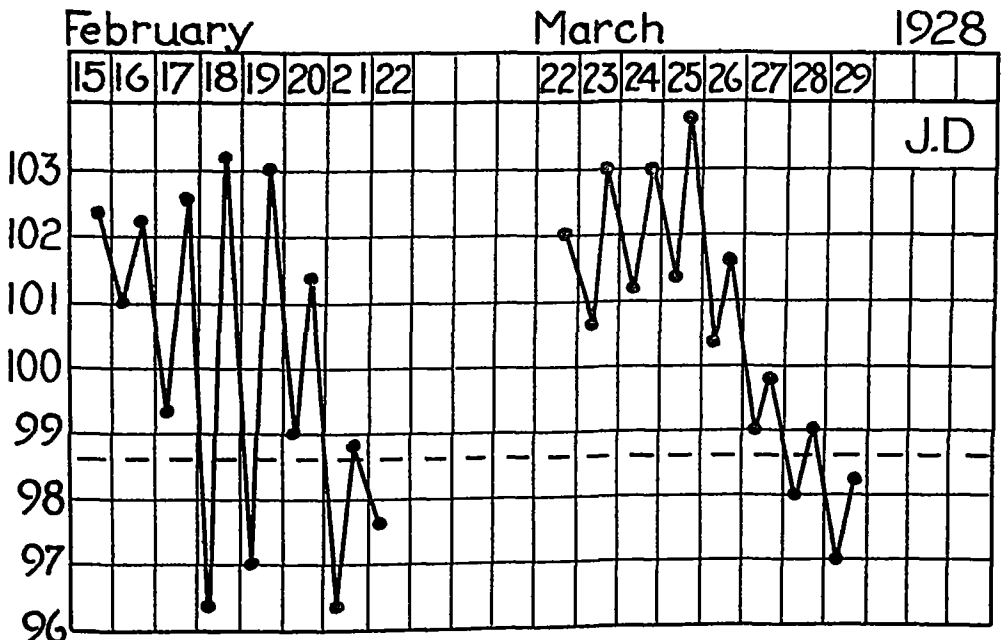


FIG 5—Chart J D From Indiana A case of the remittent malaria type, the fever would remit each afternoon with a severe chill, preceding and a heavy perspiration following The patient was quite ill but has apparently recovered at this writing

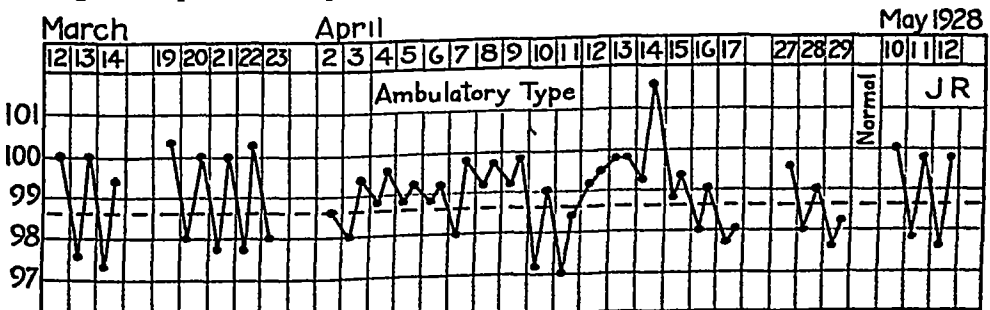


FIG 6—Chart J R From Indiana This was an ambulatory type of the disease This and two other cases continue to have undulations of fever every two or three weeks with sweating, chills and nervousness

Of the twenty-six cases which were recognized clinically, fourteen gave positive reactions to the agglutination test for undulant fever, six were negative (one test only) and blood was not sent in from the remaining six. The macroscopic agglutination test was employed throughout. Dr Francis used the three antigens, Br abortus, Br melitensis and B tularensis. The junior author employed but the one antigen, B<sub>1</sub> abortus. The agglutinin titres of the fourteen positive cases are given in Table I. It is of interest to note that the titres in fifty per cent of the tests were higher for Br abortus than they were for Br melitensis. Cross agglutination for B tularensis was slight, but observed in five cases.

In addition to the serological tests, the blood samples from the suspected cases were subjected to bacteriological examinations. Portions of the blood

clots, and the serum not used for the serological tests were introduced into recently boiled bouillon and incubated under aerobic conditions and in jars in which approximately ten per cent of the atmosphere had been replaced with CO<sub>2</sub>. For a period of one week daily transfers were made from the bouillon to agar slants but Br abortus was never isolated. The remainder of each blood clot was macerated in sterile salt solution and injected into guinea pigs. The guinea pigs were killed six to eight weeks later and were examined for the lesions, and the presence of Br abortus but with negative results in all cases. The blood of the guinea pigs never reacted to the agglutination test for infectious abortion.

The status of the dairy herd from which the entire milk supply was obtained was as follows. Twenty-three cows, seven of which gave positive re-

TABLE I—AGGLUTININ TITRES OF FOURTEEN CASES OF UNDULANT FEVER

Case No	Initials	Sex	Age	Date tested 1928	Brucella abortus No 456	Brucella Melitensis No 428	Bacterium Tularensis	Treatment of Serum
1	LF	M	22	Mar 24	1280	320	80	56° C ½ hr.
2	MR	F	19	"	1280	1280	20	" "
3	MS	M	19	"	2560	1280	0	" "
4	IT	M		"	640	640	40	" "
5	JD	M	24	"	2560	640	160	" "
6	JR	M		"	160	80	0	" "
7	DW	M	18	Apr. 7	640	640	0	" "
8	AC	F	19	" 13	320	160	0	" "
9	OR	M	25	" 14	640	640	0	" "
10	WO	M	21	" 16	2560	1280	80	Unheated no preservative
11	EJ	F	21	" 20	160	80	0	" "
12	SR	F	17	" 20	160	160	0	" "
13	M.C	F		" 21	320	320	0	" "
*14	AM	F	47	May '22	100			

\*Tested by the junior author, the other thirteen cases were tested by Dr Francis

actions to the agglutination test for infectious abortion. Br abortus was isolated from the milk of three reactors, two of which were found to have advanced cases of mastitis. The udder of a third, reacting cow was likewise affected, although Br abortus was not isolated from the milk of this animal. The cows had never been in contact with goats, and there were no hogs maintained upon the premises for breeding purposes. Adjacent to the cow lot was a pen of feeder pigs which had been placed in the feed lot as young pigs and were not of breeding age when the outbreak of undulant fever occurred.

About two months after the dairy herd was examined and corrective measures established, six of the gilts were isolated from the remainder of the pigs in the feed lot. The milk from the mastitis cases was then fed to the six gilts for a period of two weeks. (Bacteriological examination showed that two of the cows were still eliminating Br abortus in the milk.) Immediately following the feeding period four of the gilts were bred. The six animals have been repeatedly tested with the agglutination test for infectious abortion, but with negative results to date. One of the gilts had evidently conceived before the male pigs in the feed lot were castrated, since this animal gave birth to seven live pigs, nine weeks after she was segregated with the other five gilts. The pigs were killed as soon as they were farrowed and their organs examined for the presence of Br abortus but with negative results. Negative results were likewise obtained with the fetal membranes.

## DISCUSSION

Since there was no history of contact with goats or aborting hogs, is quite improbable that these animals had any direct connection with the present outbreak of undulant fever. That the infected dairy herd was directly responsible was supported by several important facts, first, the demonstration of Br abortus in the milk, second, all the undulant fever cases were heavy consumers of raw milk, with two exceptions, and these two cases cream was consumed with cereals, third, since pasteurization of milk was established no new cases have developed, fourth, the sudden outbreak among students which had assembled from a wide range of territory indicated that the infection was acquired locally and not imported.

A point of interest in the present observations is the number of clinical cases which failed to react to the agglutination test. Similar observations have been made by other investigators and serve to illustrate the fact that a single negative agglutination test is insufficient evidence to exclude undulant fever, in the face of the typical clinical syndrome of the disease. It would have been of scientific interest to have been able to isolate Br abortus from the blood-stream of some of these patients but since this was not accomplished, the results should be interpreted as an absence of bacteremia and not as the absence of Br abortus as the etiological factor.

The tendency of some investigators to consider swine as the reservoir of infection is not supported by the present observations. The failure to

infect gilts by feeding milk which was shown to contain *B. abortus* must be considered as evidence that the organism concerned in this instance was not the porcine type. Furthermore, the cultures of *Br. abortus* which were

isolated from the milk have been found by both the junior author and Dr I. F. Huddleson,\* to be of bovine type

\*Personal communication



# Report of a Case of Primary Multiple Myeloma With Bence-Jones Protein in the Pleural Effusion

By EUGENE E. MARCOVICI, M D , F A C P , *New York City*

**J.** H. CORIAT in 1903 described for the first time the occurrence of Bence Jones protein in the pleuritic effusion of a patient suffering from Korsakoff's psychosis, with extreme tenderness of the ribs and no albumosuria

The case I wish to report has been under my observation from Dec 13th, 1927, till to its exitus on April 13th, 1928. The history presents the following data. Mrs Th B, 55 y old, born in Fubine, Italy. Mother died at the age of 40 due to some form of anemia. Father died at the age of 70, after apoplexy. One sister 60, a brother 65, both well. Patient menstruated at the age of 14, married at 18, had six children, all well. Her husband died at the age of 40 from Bright's disease.

Patient's normal weight was about 100 lbs, had worked very hard and was poorly nourished. Outside of constipation, the patient did not remember any serious ailment.

In February 1927, the patient felt neuralgia-like pains over the left side of the chest, most of the ribs were sensitive at the slightest pressure. No fever, appetite poor.

In April she went to the farm of her brother in Connecticut for a rest, while carrying a pail of water, she felt a sudden pain in the left side of the chest, similar to the breaking of some ribs. In August 1927 the patient came back to the city. The pains were rather increased, severe shooting pains in most of the ribs, on the left side and over the heart region. No appe-

tite, always constipated. Loss of weight of about 12 lbs, sleep very poor.

In October 1927, the patient had X-rays taken of her chest, report not known to the family. In November at the Reconstruction Hospital, where I saw the patient in consultation, they were of the opinion that primary carcinoma of the cecum was the probable diagnosis and that the rib conditions were carcinoma metastases. I found then no signs of malignancy in the intestinal tract.

On December 13th the family brought the patient to my office for another examination and further treatment.

She complained of severe pains in the left side of the chest, poor sleep on account of the pain, sometimes night sweats, seldom cough. Walking was difficult, weakness, lack of appetite, gradual loss of weight, constipation, no nausea. Shortness of breath, sporadic pains, redness and slight swelling of the right toe and the right trochanter. Headaches mostly forehead, no dizziness. Paresthesia in both forearms. Pt was pale, prematurely aged, and poorly nourished, weight 89 lbs, Temp 99.6°, Resp 36, Pulse tachycard 104, Blood pressure 110/80. Dyspnea. Blood examination E 4475000 L 13150 Hemoglobin 85%. Differential leucocyte count. P 72, L 31, 11, E 2, Ba 2, n Mye 10. Urine examination. Albumin in traces, Sugar neg. Bence Jones protein neg. Sediment no casts, few epithelial cells and WBC. The head was carried inclined toward the left, the muscles of the neck were contracted (not a recent condition), possibly following

a rheumatic myositis The face was wrinkled, pale, emaciated Panniculus adiposus was absent The head nerves were normal The tongue was not coated, slightly dry The neck organs were normal Pharynx and larynx did not show any peculiarities No gland enlargements, the veins were not distended The chest looked very narrow, the breathing appeared superficial and frequent

The lower intercostal spaces showed retraction during inspiration, the right side of the thorax expanding less than the left, basal adhesion left, dullness over the right lower lobe Both apices retracted There was vesicular breathing over the apices, no râles, over the right base were friction sounds, over the left lower lobe reduced breathing sounds, no râles or friction

The fluoroscopic examination of the chest, showed that several ribs have undergone a destructive process, especially the fifth right rib and the third, fourth and fifth left rib The right hilus showed a great amount of infiltration, in the shape of an interlobar effusion The right base showed adhesions The heart of normal size, the sounds clear, the pulse rhythmical, equal but rapid

The examination and palpation of the abdomen did not show any pathology The diagnosis made at my office was multiple myeloma of the ribs and advised that the patient be placed in the hospital for observation

The patient has been under very careful observation The temperature had been normal up to the time of her admission, when it reached 101.6 F Upon examination I found an accumulation of right pleural effusion The X-ray examination by Dr Pound on January 9 reports the following findings Films were made of the skull, forearms, femurs, legs and feet There was no evidence of any pathological changes in the bones or the periosteum Films of the colon after a barium enema showed no evidence of cancer or obstructive loops or kinks Film of the chest showed the lower half or two thirds of the right chest filled with a pleural effusion The fifth left rib showed complete destruction of all of the bony portion except the extreme anterior end The

sixth rib left posterior axillary line showed a destruction for a distance of a trifle over an inch The seventh rib posteriorly showed several small punched-out areas The tenth rib left showed destruction of the posterior two thirds There were a few areas of pleural involvement in the left chest (Fig 1) Diagnosis Multiple myeloma

On January 9, the temp was 101.6 F. The urine was negative for Bence Jones, the blood count findings were as follows: E 450,000 L 15,100 Hem 100%, P 85, L 12, E 1 The pleural effusion reached the spina scapulae The fluid obtained through paracentesis had a specific gravity of 1.024, the reaction for Bence Jones protein was doubtful (Wells, Chem Path, W B Saunders Phila 1925, p 597) The X-ray report (Dr Pound) on the day after the paracentesis, Jan 10, read: Pleural effusion has been removed through tapping Considerable amount of fluid has been removed The sixth rib on the right side in the axillary line showed a destruction for a distance of an inch and a half (Fig 2, Fig 2a)

The blood count on Jan 10th was L 15,000 P 81, L 5, E 1, 17, Ba 2, n Mye 4

On Jan 11th L 10,000, P 77½%, L 6, 1 7½%, Mo 1, Trans 0.5%, E 1, Ba 1%, Myel 1½%

On Jan 14th the temp was 99.9°, the leukocyte count 8200, P 73, L 12, 1 3, Mo 2, E 4, Ba 2, Mye 4

On Jan 18th, leukocyte count was 8000 P 68, L 7, 1 8, Mo 7, Trans 3, E 15%, Ba 15%, Myel 2

On Jan 21st, L 10,000, P 73, L 11, 1 5, Mo 4, E 4, Ba 1, Myel 2 The fluid in the chest had collected again The X-ray report as follows: Effusion in the right chest has reaccumulated There appeared to be a number of punched-out areas in several of the ribs, which showed no previous involvement The sixth rib showed further destruction in the posterior portion (Fig 3)

On Feb 8th the X-ray report read: Pleural effusion filling most of the right chest, several small areas of pleural thickening (Fig 4) Blood report Hem 80%, L 5,000,000, L 8000, P 69, 1, 1, 12 Mo 2, E 2



FIG 1



FIG 2



FIG 2a



FIG 3

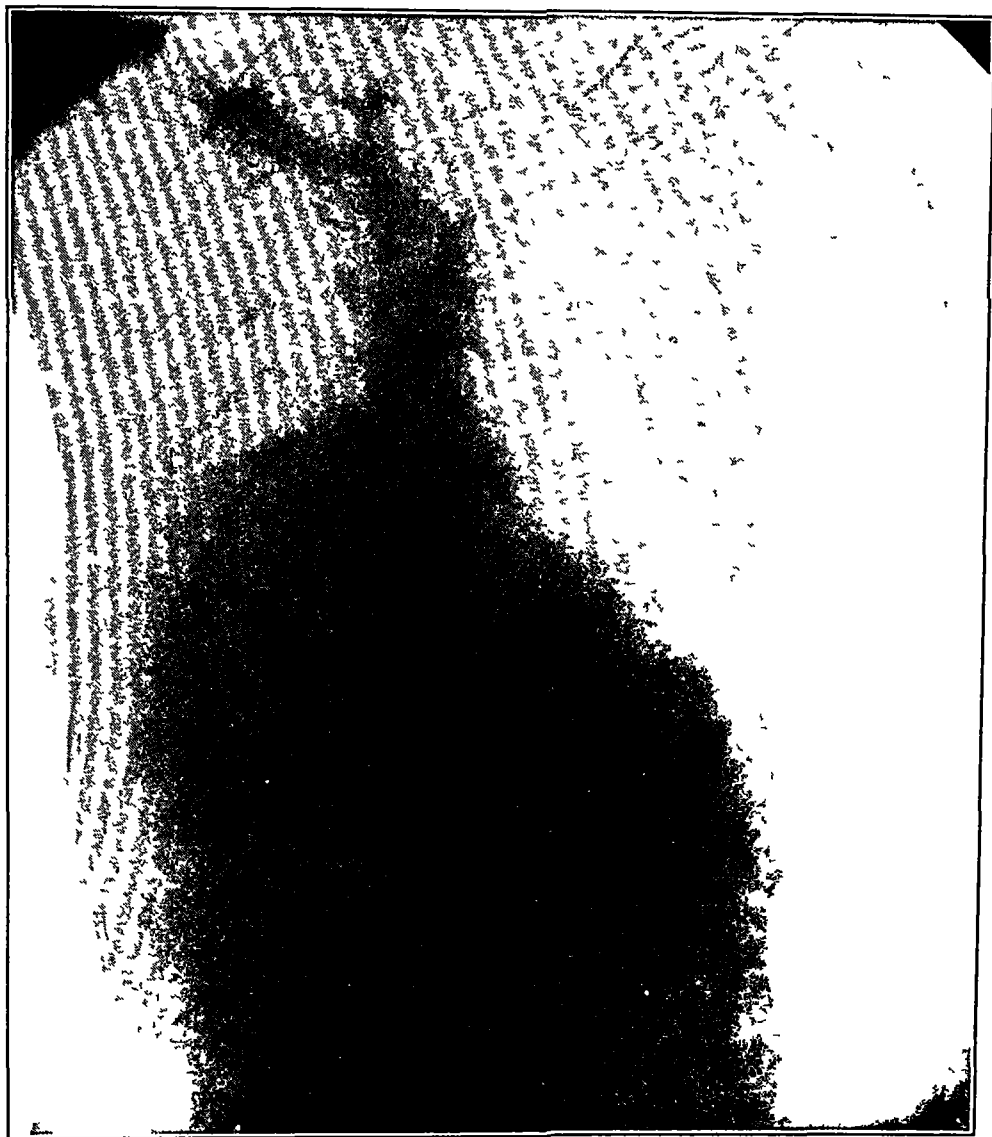


FIG 4

On Feb 10th through paracentesis 1200 cc of fluid was removed, the specific gravity was 1024 *The Bence Jones reaction was positive* (Dr Killian)

On Feb 14th the blood report was Hem 94%, E 4,500,000, L 5000, P 71, L and 125, Mo 2, Bas 1, E 1 The blood chemistry Urea N 17.1, uric acid 1.5, sugar 68 mgr

On Feb 21st, 1928, the X-ray report says more pleural involvement in the right chest with further destruction of the ribs previously noted The fourth and sixth ribs on the left side showed an increased destruction (Fig 5)

On Feb 26th, patient complained of pains in the lower ribs on both sides The examination proved both fifth ribs very sensitive to touch The cachexia is progressing rapidly Still the blood report does not show any anemia Haem 85, E 5,500,000, L 7100, P 74%, L and 1 19%, Mo 3%, E 4%

While the patient used to move around her room, and sometimes sit for few hours in a chair, she now keeps quietly in bed, avoiding any other position than the one of lying flat on her back

On March 2nd, I made a more thorough inquiry about her condition and a renewed complete examination The complaints were a shortness of breath which is less intensive when the pains are localized in the upper back (shoulder and shoulder blades) than when they involve the lower right ribs A certain catching of the breath, corresponding to the lower left ribs, is always present, whereas at the beginning of the disease, was only of short duration No appetite, nausea quite frequently Constipation, but no pains in the abdomen, unless after a laxative There is no burning passing the water but she has to void often No cough, sleep very poor, unless with the help of hypnotics Patient complains also of a tired feeling in the arms, more so than in the legs The motion in the arms gives pains in the chest The speech is quite difficult, partly through shortness of breath Walking is very difficult, with increased dyspnea and choking feeling While sitting in a chair the patient has pains in

both lower parts of the chest, left more than the right, the right trochanter is also painful (the mentioned spots and sometimes the right and left big toe would become very painful for a short period of time, showing redness on the surface and a certain amount of swelling, like in gouty attacks and then disappear, with no X-ray findings) There is a numbness in both arms Examination shows temp 98.8°, blood pressure 110/80, pulse 104 Patient is sitting in a chair, appearance cachectic, dyspnea, frequency 36 The inspection of the chest shows great emaciation, the scaleni and pectoralis muscles pulled strenuously with every breath, the intercostal spaces show inspiratory depressions The whole chest very sensitive to touch, especially the lower ribs, the lower part of the sternum, the processus spinosi of the 1st, 2nd, and 3rd dorsal vertebrae The percussion gives dullness from the upper margin of the third right rib and from the middle of the scapula down Compression breathing to be heard over the third and fourth intercostal spaces, no breathing sound or vocal fremitus over the dull part of the right chest The left lung base adherent from a previous basal pleurisy, the breathing sounds over the left lung negative The heart action is very fast, no murmurs, no arrhythmia The abdomen meteoric, due more to the opiate the patient gets in order to obtain some sleep, than to any other source The parasthesia of both arms, left more than the right, is very pronounced

On March 6th the fluid in the right chest has reached anteriorly the lower margin of the right second rib and the spina scapulae posteriorly Through renewed tapping of the pleural cavity 800 cc of fluid was obtained Blood was taken the same day for the detection of Bence Jones protein in the serum Report on Bence Jones protein (Dr Killian) was positive in the chest fluid faintly positive for the blood serum

X-ray examination on March 7th reports pleural effusion still present in the lower right chest Advanced destruction areas in the left ribs, sixth rib on the right shows increased destruction (Fig 6)

Blood examination report Hem 85





FIG 5



FIG 6



FIG 7

E 5,000,000, Leukocytes 7800, P 63, L and 1 32, Mo 4, E 1 On March 23rd Hem 85%, E 5,000,000, L 12,000, P 78, L and 1 17, Mo 2, E 2, Ba 1

March 25th the dyspnea is increasing, excessive pains in the lower left ribs, pt very restless, morphine needed every night to induce some sleep

On March 26th another paracentesis was performed, 800 cc of fluid was obtained. The dulness decreased to the upper margin of the sixth right rib anteriorly, and to the angulus scapulae posteriorly. Breathing was easier. Temperature normal, Pulse 120. Blood was also taken and the bloodserum showed a positive reaction for Bence Jones protein, as did the pleural fluid. The urine of the same day, for the first time since the beginning of the observation, was positive for Bence Jones protein, 291%. The X-ray report, from pictures taken after the removal of the fluid on March 26th, reads: Pleural effusion remaining in the right chest. There is a mass around the right root about the size of an egg, which has been present throughout the series but shows more definitely in the recent films, the fourth rib left shows more destruction and the sixth rib on the left side is practically destroyed. There are numerous changes throughout the chest (Fig 7)

*Diagnosis (Dr Pound)* Multiple Myeloma with progressive rib destruction, pleural and lung involvement

The blood count on April 6th Hem 96%, 5,000,000, leukocytes 9100, P 72%, L and 1 27%, Mo 1%

The temperatures to April 12th were normal. The cachexia rapidly progressing, the pulse getting faster and irregular, the patient refuses any nourishment. The pains were so excessive that we had to keep her the last days under morphine. After a comatose stage of one day, the patient died on April 13th, 1928.

The post mortem was not possible, not having the consent of the family.

The therapeutic measures during the time of her illness were roborantia, quartz light, camphor in oil and mirion, with no advantage. The deep X-ray therapy as one would suggest has not met with the

approval of the specialist in the case, the conditions being too advanced. Intravenous Thorium X injections, which I would have liked to try, were not available. There is certainly for myeloma a more definite impossibility to reach any therapeutic success than in any other malignant tumor.

The differential diagnosis from secondary multiple myeloma was the absence of the primary tumor, from tuberculosis of the ribs with pleurisy, the absence of any tuberculous symptoms, from rachitis, osteomalacia, osteitis deformans, caries of the vertebrae, isolated vertebral tumors, the X-ray findings and the absence of the Bence Jones protein in the urine. Senile osteoporosis leads also to spontaneous fractures, the pains are not very intense. Chloroma has a leukemic blood picture, and the localization is mostly in the flat bones of the skull.

The most characteristic symptoms for myeloma are Bence Jones protein in the urine, the cachexia, the spontaneous rib fractures and deformities and the intensive periodical pains, the X-ray findings, the recurrent fever, the absence of any too pronounced changes in the blood with the exception of the slight myelocytosis and the presence of basophiles (common occurrence in all malignant tumors).

## CONCLUSIONS

The reported case of primary multiple myeloma presents certain peculiarities, which may be of interest.

The ribs alone were found affected, in none of the other bones were tumor formations detected. The destruction of the ribs led to the pleural effusion, not a common occurrence.

The pleural fluid contained Bence Jones protein.

The blood serum and the urine contained also Bence Jones protein, the urine only toward the end of the patient's life.

The X-ray examinations have helped to the early diagnosis, when



FIG 8

the other symptoms were not evident as yet

The hematological findings in this case were Normal hemoglobin and red cell count, a normal leucocyte count in the fever free period, a slight leukocytosis with the accumulation of the pleural fluid. An increase in the percentage of the eosinophiles (to 5%), of the basophiles (to 4%), the appearance of neutrophilic myelocytes (up to 6%), a polynuclear leukocytosis with the pleural complication

The recurrent type of fever since the appearance of the lung complication

The temporary pericostal inflammation over both trochanter and the big toes

Paresthesia of the upper extremities

The progressive cachexia

The duration of the disease since the first symptoms, has been a little over one year. The early diagnosis by means of X-ray should be attempted in every suspicious case (some are taken for intercostal neuralgias) and deep X-ray therapy, radium or mesothorium irradiations tried from the beginning. Intravenous injections of Thorium X are supposed to be of value

The therapeutic measures in this case were of no value. I have used quartz light, arsenic and iron, morphia, sedatives and narcotics toward the end were unavoidable

The multiple myeloma damages the bone marrow, the most important blood producing organ. While in some instances the multiple myelomas



FIG 9



FIG 10



FIG 11



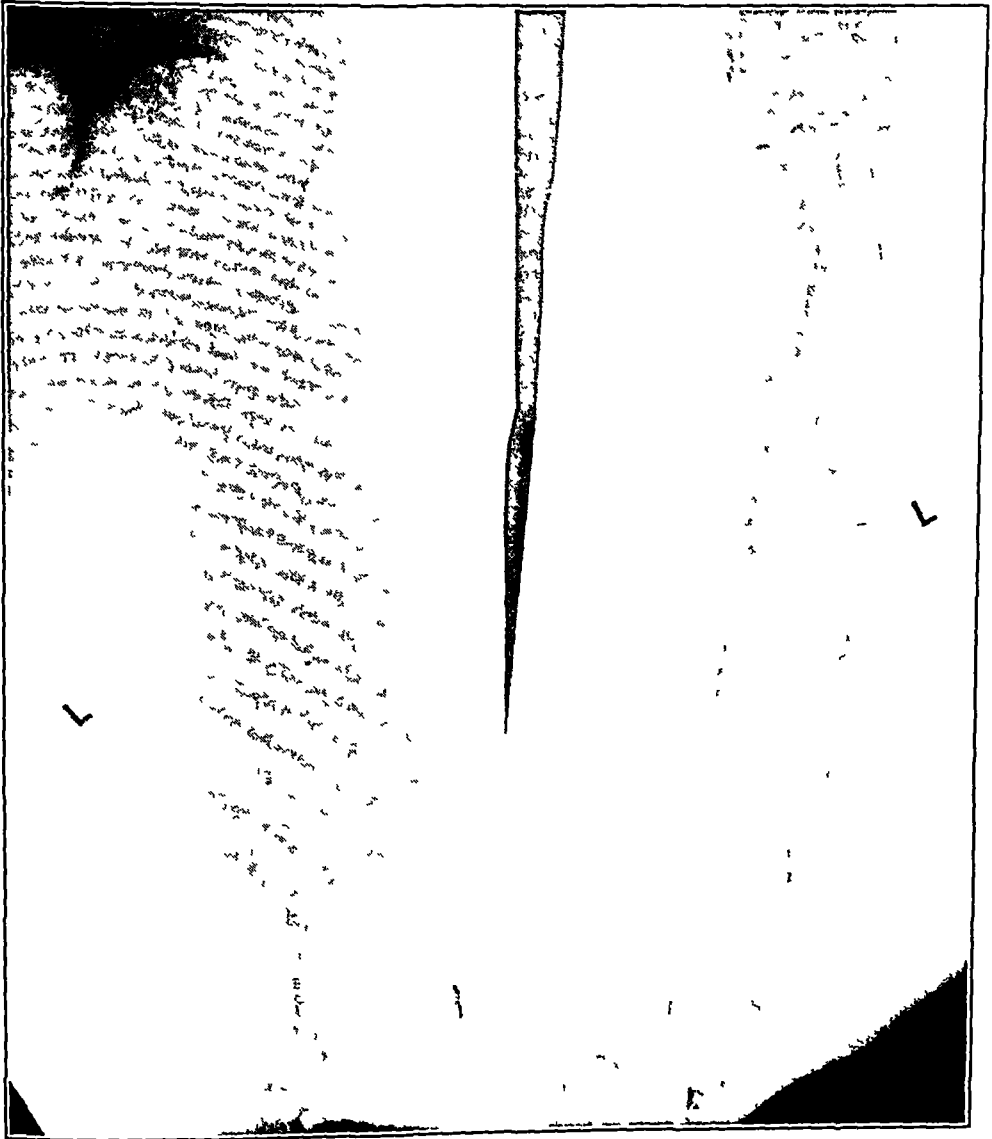


FIG 12

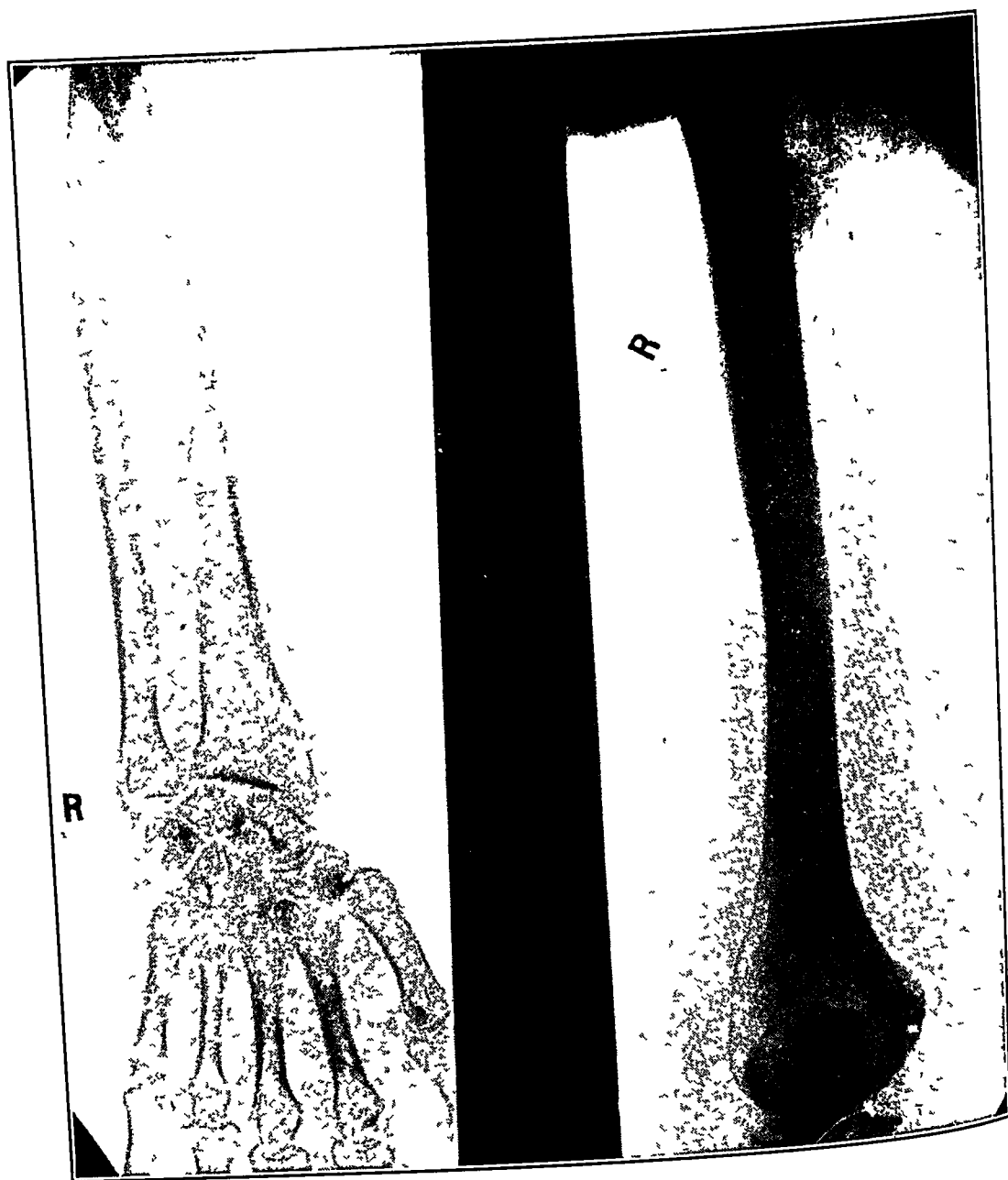


FIG 13

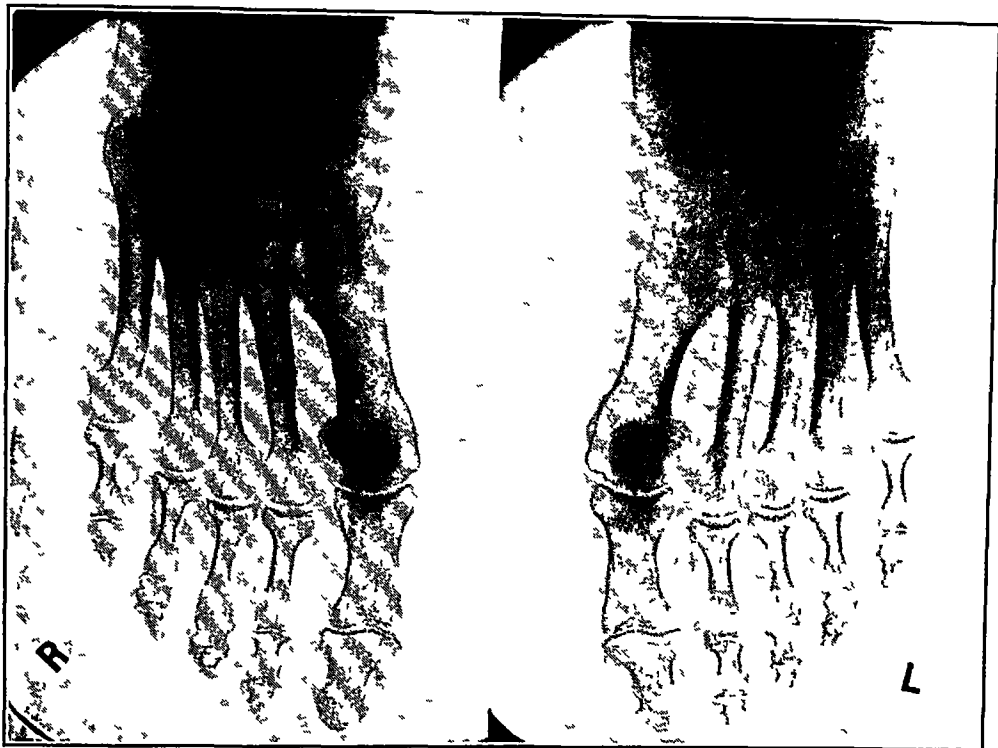


FIG 14

differ in their clinical manifestations from the secondary multiple tumor formations in the bone marrow, in others their clinical picture is identical

The myelomas, depending upon their localization and distribution in the skeletal system, upon the intensity and direction of their growth, their anatomic relation to the compact bone substance present a diversity of symptoms

In some cases the symptom complex is very characteristic (Kahler) very severe pains, neuralgic like, over the thorax mostly in the ribs appearing in periodic intervals of several days. Sometimes, a deviation of the spine, or a definite kyphosis, the patient appearing smaller, will make the differentiation from osteomalacia

difficult. The ribs fracture at the least physical effort

Secondary to such fractures a pleural effusion may follow (an exudate through inflammation of the pleura) accompanied by fever

The elimination of the Bence Jones protein, which appears in the urine of 80% of the myeloma cases, although sometimes toward the end of the patient's life usually one of the first symptoms, is regarded as the cardinal symptom of the disease. There is a very pronounced cachexia. The blood findings, as described in the literature, show little pathology except anemia.

Kahler in 1889 first described the above symptoms of the disease and held the circumscribed homologous tumor formations of the bone marrow responsible for the clinical symptoms

of the disease. The histological examination of his case (Chiari), showed that the tumors were multiple endotheliomas of the bone marrow. Further research has shown that primary multiple myelomas of various histological structure present the same clinical picture.

The case of Kahler was of a physician, 46 years old, whose disease started in 1879 with pains in the right side of the chest, which increased during respiration. The pains disappeared gradually, (few days), and returned after months localized in one point of the right 3rd rib, disappearing again after four weeks,—till 1880, in April, when the pains appeared in different regions, (ribs, vertebrae, left shoulder, left upper arm), increasing during motion. The processes spinosi of the vertebral column were sensitive. In March, 1881, a swelling appeared in the left fifth rib, which subsided after several weeks. Such periodic swellings, in different ribs, occurred often in the next years. Several nerve plexi became sensitive. In the urine the Bence Jones protein was positive. In 1882, the fingers of the hands, the crista ossis ilei and the back of the head, became very painful, the gradually increasing cachexia forcing the patient to stay in bed. Paresthesia of the lower extremities, cardialgia and vomiting, enteralgia and asthmatic attacks, paroxysms of cough and chills complicated the condition. In the sixth year of the disease, a kyphosis in the upper dorsal segment started, the thorax became short, the vertebral column bent over more and

more, the chin showed a decubitus from pressing on the chest.

The third right rib fractured spontaneously. Finally came disturbances of the sensorium, hallucinations and loss of consciousness. The cachexia became very pronounced, though still only a slight anemia.

Patient died after 8 years of illness. The post mortem showed numerous bone tumors which were called multiple myeloma. (Chiari held them for multiple bone endotheliomata).

### ETIOLOGY

Trauma has been advocated as etiology by Gluzinski and Reichenstein, Heldt, Simmonds, Schennan, Weiss, Winkler, pains before the trauma, in some cases, a long interval between trauma and symptoms (Hopkins and Savory, Marchand, Funkenstein), trauma and symptoms at the same time, in the case of Ewald's rib fractures in Versé's case, where trauma happened 5 months previously. No trauma mentioned in Wallgren's cases. Infections accepted as etiology by Bechtold, Klebs.

Infections with fever in the cases of Hammer, Charles and Sanguinetti, Ellinger, Seegelken, Vignard and Gallavardin, v Rusticky, Wieland and Zahn. The type of fever intermittent, due to the bone marrow process (Winkler), to bacteria in the blood (Beck and McClearly), or in diseased parts of the bone marrow (Bender, Madsen). Lues in the case of Bertoye. Lues and myeloma (von der Heide, Madsen, Wright, Parkes Weber).

Tuberculosis of the lungs (Abrikossoff, Zahn, Madsen, MacCallum,

Scherman, Saltykow, Taylor and Miller)

Primary anemia was thought to be the cause of the bone marrow changes by Grawitz

In the case reported the history mentions a form of anemia in the mother and trauma at the beginning of the disease (the rib fracture which followed the trauma, the bone marrow condition may already have existed)

The age between 50 and 55 is most frequent for myeloma cases, as seen in Wallgren's table, reporting on 98 cases of anatomically certain myeloma, the youngest case at 22 (Haberfeld and Lordy), the oldest described by Grosch in a 80 years old woman. The disease is more frequent in men

#### PATHOLOGY

According to the histological structure we distinguish two groups of primary multiple tumors of the bone marrow

(a) the true multiple myeloma, circumscribed, the cells of which appear normally in the bone marrow tissue (parenchyma cells, colorless blood cells or normoblasts)

(b) the second group of primary multiple bone marrow tumors which have their origin in the stroma of the bone marrow (connective tissue or blood vessels) sarcoma, endothelioma, enchondroma

The skeletal system in primary multiple myeloma presents deformities and spontaneous fractures. The thin corticalis at different places may resemble parchment. The tumors are mostly round, circumscribed, well demarcated from the surrounding bone marrow, gray, red or yellowish in color, resem-

bling in sections, the structure of lymphatic glands. The most frequent localisations are the ribs, the vertebrae, and the flat bones, which contain red marrow. The tumors grow often in the compact portion of the bones, replace it and push the periosteum out forming round deformities. In other instances the tumors do not grow in the compact bone substance and do not produce deformities, they can only be detected within the bone marrow by sawing the bones. In the former instance, the bones are very soft and easily breakable (the ribs especially), the tumor mass having the consistency of white brain matter or spleen pulp. Often in post mortem, on a superficial observation of the skeletal system, serious changes are found, although one cannot macroscopically distinguish between the true multiple myeloma and the histologically differently constructed primary multiple bone tumors.

The presence of multiple myeloma is detected through bone enlargements, especially of the ribs, also the skull, sternum and hip bones. In the vertebrae and large bones the tumors are not protruding, in the case of involvement of the vertebral column, only if the protrusion effects a compression of the spinal cord does it become clinically interesting.

The sternum may become quite thick through the presence of tumor mass. Kyphosis and kyphoscoliosis of the vertebral column are also a frequent occurrence.

The term "multiple myeloma" was given by v. Rustitzky in 1873. He studied histologically and described one case from von Recklinghausen's

Institute The tumors in his case had the consistency of white brain matter and presented the appearance of hypertrophied lymphatic glands. Microscopically the tumors were formed of round cells with an opalescent protoplasm and one or two round nuclei, little different from the surrounding bone marrow cells. On account of the identity of the tumor cells with the bone marrow cell elements, Rustitzky named the tumors myeloma, and wanted to emphasize that they have nothing in common with the myelogenous bone sarcoma (Virchow), which show a great many giant cells. The fact that the multiple bone sarcoma grows in the surrounding tissue, while the myeloma is strictly limited to the bone system, is another differentially diagnostic important feature.

Zahn in 1885, finds the analogy between myeloma and leukemic or pseudoleukemic hyperplasia, naming the former myelogenous form of pseudoleukemia.

Sternberg while he admits analogous changes of the bone marrow through myeloma, as the ones in the lymphatic glands and the spleen through pseudoleukemia, places myelomas on account of their localization and appearance in circumscribed, tumor-like formations, among the tumors, and due to their anatomohistological peculiarities, distinguishes them from pseudoleukemia.

Naegeli agrees to the similarity of myeloma with aleukemic systemic affections.

Grawitz describes them under the chapter of aleukemic medullary hyperplasia.

Lubarsh sees in myeloma a systemic disease, very close to the leukemic and pseudoleukemic affections.

Schüdde in his chapter on "The Blood-forming organs," describes myeloma as true bone marrow tumors, tumor-like hyperplasias of myeloid tissue, not easy to distinguish from leukemic myeloses (Myelosarcoma are those tumors, which while made of myeloid tissue, produce metastases in other organs).

Kaufmann calls multiple true myelomas primary tumors of the bone marrow, composed of bone marrow cells.

Ribbert says "In its structure the myeloma is close to lymphocytoma."

Pappenheim calls multiple myeloma a medullary form of pseudoleukemia, a systemic disease of the hemopoietic apparatus, of aleukemic nature.

Histologically, according to the kind of cells composing the myeloma, there are six different types of myeloma — 1) Myeloma composed of lymphocytes 2) of myelocytes, 3) of myeloblasts, 4) of plasma cells, 5) of erythroblasts, 6) a mixed myeloma, in which all bone marrow cells are represented.

There is a definite differentiation between the medullary pseudoleukemia, which does not affect the compact portion of the bones, and the true multiple primary myelomas, which destroy it through a progressive resorption. The cases in which this peculiarity is not mentioned may have died before the growth of the myelomatous tumors was strong enough.

From the pathological histological point of view we define primary

multiple myeloma as tumors localized in the bone marrow, mostly circumscribed leukocytomas, having a tendency toward malignant growth but seldom leading to infiltration of the surrounding tissue or producing metastasis. Under certain circumstances they may not appear as isolated systemic diseases of the bone marrow, but rather, of the whole hemopoietic apparatus.

This purely histological definition should not lead to conclusions of any etiologic relation between multiple myeloma and the leukemic or aleukemic conditions.

#### CLINICAL SYMPTOMS

The symptomatology of the primary multiple tumor formations in the bone system is practically the same, independent of the histological structure. The beginning of the disease is hardly noticeable. The patient very seldom knows the exact time when the first symptoms appeared.

In *Zahn's* case, intense pains in the region of the lower ribs and lumbar region followed exposure and strenuous work.

In *Hammer's* case, headaches were the first symptom, possibly due to the primary localization of the tumors in the bones of the head. In other cases, the pains started in the bones of the extremities or in the spinal column. Such conditions are apt to be regarded as rheumatism.

Often a trauma is given as history, and the disease followed, supposedly, several weeks afterwards, (cases of *Winkler*, *Ewald*, *Abderhalden* and

*Rostoski* (after lifting a heavy load), *Gluzinski* and *Reichenstem*, *Hoffmann*, *Vance*). The trauma cannot be accepted as etiology, but helps to disclose the existence of the disease and the course may be hastened. The periodicity with which the pains appear and the pain-free intervals are characteristic. The localization is for the most part, in the thorax, vertebrae, hip bones, long bones, and only seldom in the head.

Cachexia very soon becomes pronounced but there are no signs of anemia.

The most evident symptoms are the bone deformities, such as deviation and bending of the spine, thickening of the ribs with nerve compression, and spontaneous rib fractures. Thoracic deformities which impair the circulatory and respiratory functions produce dyspnea and cardiac oppression and may lead to secondary inflammatory conditions of the lungs, and so, to exitus, also, tumors in the vertebral column, with compression of the spinal cord, tending thus to exitus. The patients reach the state when they cannot leave their beds develop decubitus and die from some complication.

The duration of the disease is on the average, from six months to one and one-half years, although there are exceptions, as in *Marchand's* case, which lasted six weeks, or in *Sussmann's*, which lasted three weeks, or in *Kahler's*, when the patient lived eight years. Men are more frequently affected than women, and generally between the ages of forty and sixty years.

## BONE SYMPTOMS

The tumors may not be detected intra vitam if they are very small or very few in number and do not produce any symptoms. Only in post mortems are multiple myelomas found in cases where they were not suspected.

The pains start in one bone and are most intense if the process involves the thorax, especially the ribs, giving a feeling of great oppression. The pains appear periodically or intermittently, increased through exertion. A severe sensitiveness of the bones is noticeable during pain paroxysms and also later. The intensity of the pains can be so great that the patient must keep to one position.

The patient of *Abrikosoff* started, as in my case, with pains in the left lower ribs, especially during motion. The percussion in such cases is painful.

The prominent symptoms (*Sternberg*) are,—very painful thickening of some of the bones,—sternum, ribs, skull, hip bones. The bone changes are seldom so evident as to be seen from a distance, except as in *Rusticki's* case, in which a tumor the size of a bean appeared on the left temporal side. It grew to the size of an apple, displaced the eye, injured the sight, perforated the bone and adhered to the dura mater.

Angular bending of the ribs occurs when the corticalis gets thin through the growth of the myeloma. Also, bending of the vertebral column, reducing the height of the patient, as in *Kahler's* case, who shrank to midget size. *Sternberg's* case had thorax deformity, the sternum S-

shaped, and the vertebral column in a half circle.

The nerve plexi can be damaged through pressure, with resulting paraesthesia and nerve paralysis. In myeloma of the skull a stuporous condition is a usual symptom. Compression myelitis (*Rusticki's* case) is followed by paraplegia, incontinentia alvi and urinae.

Spontaneous fractures of the ribs caused by moving in bed or by percussion or palpation, are a frequent occurrence, and they represent the early symptoms of the disease.

*Kahler's* patient suffered immensely from the slightest motion and even from breathing.

## SYMPTOMS OF THE NERVOUS SYSTEM

The nervous disturbances accompanying multiple myeloma may be the result of direct pressure of the tumors on a nerve plexus, the central nervous system, or in other cases of a toxic nature.

Paraesthesia is always a common complaint. Severe pains are localized in the bones seldom corresponding to one nerve. Skin hyperalgesia is a common symptom. Most important are the disturbances caused through compression of the spinal cord, followed by paraplegia, incontinentia alvi et urinae. Anomalies of reflexes are mentioned, without a definite pathology.

*Stokvis* mentioned in his case, paraplegia, speech and swallowing disturbances, salivation, trigeminus and facialis paralysis.

*Wieland's* case had hearing disturbances (labyrinth diseases).

*Rustitzky's* case started with a tu



mor in the right temple, which gradually displaced the eye

Quackenboss and Verhoff describe the protusion of the eye bulb through tumor pressure

### HEART AND LUNGS

The deformity of the thorax will bring about pressure symptoms of the heart and lungs

Terminal pneumonias are quite frequent and also hydrothorax

The digestive organs present also anomalies as anacidity, lack of appetite and intestinal paralysis (through direct cord lesions)

Cachexia is one of the most important symptoms, sometimes pronounced before definite bone symptoms are detected. A very severe general weakness, which begins early and progresses rapidly is another specific occurrence. The extremities are mostly affected, which forces the patients to leave the bed as little as possible

The temperature is mostly normal, although there are instances, where a recurrent fever appears, sometimes chills and sweats, (Hirschfeld)

### BLOOD FINDINGS

The bone marrow in myeloma is replaced to a great extent by tumor masses, some parts, through pressure, being transformed into red marrow, we would expect serious changes in the composition of the blood

A slight anemia is mentioned in most of the cases (Anemia reported by Austin, Beck and McCleary, Conti, Ellinger, Gluzinski, Haberfeld, von der Heyden, Jacobson, Kahn, Kim-

merle, King, McCallum, Madsen, Mieremet, Schutz, Sexsmith & Klein, Stumm, Weber, Weinberg and Schwartz, Wallgren (5 cases among 14)

Normal findings reported by Bombard, Christian, Thomas, Jellineck, Kahn, McConnell, Martini, Scarlini, Vance, Wright, Wallgren (5 cases)

The hemoglobin is found reported as low as 30% by Hertz and Jochmann-Schumm, 23% by Parkes. Weber Normoblasts and megaloblasts are mentioned by Gluzinski and Reichenstein. Lymphocytosis up to 60% and normoblasts in Voit-Salvendy and Hirschfeld cases

Myelocytes, as pathological cells, are cited by Saltikow, Sternberg (21 8%), Parkes, Weber, Wallgren. Eosinophilia cited in 6 cases by Wallgren

Conti in his case mentions Hem 48%, Erythr 1900000, L 3400, (P 42%, E 4%, Ba 2%, L 14%, I 10%, Mo 22%, Myel 6%)

Arneth in his case found Hem 42%, E 2400000, L 10000. The percentage of the neutrophile polymorphs, was normal

Kahn reports a pronounced anemia in two cases 1) Hem 34%, E 3200000, L 10200, (P 63%, L and I 35%, Mo 2%)

2) Hem 30% E 2000000, L 4800, (P 49%, L 42%, Mo 9%), later Hem 18%, E 1584000 L 4200 (P 60%, L 36% Mo 3% Ba 1%)

Roman in his two cases observed in children, finds Hem 28%, E 1900000 L 9400 (P 26, 8% E 16% L 63 8% Mo 58%, Myel 2%) and Hem 40%, E 1500000,

L 9600 (P 22%, L 65%, Mo 8%, Myel 5%)

Sexsmith, found Hem 85%, E. 3140000, L 8000, (P 56%, L 22%, Frans 18%, E 4%)

Martini, found Hem 70%, E. 4877000, L 6000, P 61%, E 1%, Mo 10%, L and 128%)

Kimmerle in his case Hem 70%, E 3760000, L 5700 (P 60%, L 30%, Mo 6%, E 1%, Trans 3%).

McCallum reports as findings Hem 52%, E 3548000, L 4500

McConnell Hem 80%, E 4720000, L 7200 (P 58%, L 7%, L 30%, Trans. 5%)

#### THE URINE

There is not another disease of the hemapoeitic apparatus, in which the urine reports are of such importance. In some cases there is albumin and cylindruria, in a large percentage the appearance of the Bence Jones protein is of chief value. Up to 1910 (cases collected by Hirschfeld) 36 cases mention the presence of Bence Jones protein in the urine, while in 42 cases it was not detectable (in some, they may have neglected to look for it, in others the diagnosis of myeloma has been made only after post mortem)

Decastello found the protein in 2 cases of lymphatic leukemia, Askanazy also in a case of leucemia. Campbell Horsfall reports the presence of the protein in a case of gunshot under the knee, Zuelzer in dogs poisoned with pyridin

The substance will be found in diseases involving the bone marrow, seldom in leukemias, most frequently in multiple myeloma. The cases of

Fitz (myxedema and albumosuria) and of Coriat (Bence Jones protein in the pleural exudate of a case of Koisakoff's psychosis and myeloma), are doubtful in the opinion of Hirschfeld

Bence Jones was the first in 1848, in a case of myeloma of Dalrymple and MacIntyre, to detect a protein which appeared in the urine, when heated to a temperature of 50 to 60 C, and which became soluble at a higher temperature (the case was diagnosed as osteomalacia fragilis rubra)

Stokvis in 1869, mentions the presence of the protein in a case of osteomalacia, Rustitzky in 1873, Kähler in 1889, Kaschker in 1894, report it in cases of senile osteomalacia

Seegelken in 1896, in a case of chondro-sarcoma with albuminuria, Senator, Rosin, Süßmann, in 1897 in clinically evident cases of multiple myeloma

Magnus Levy, in 1900, studied thoroughly the substance and found it to be a protein, not an albumose. Since then, we speak of a Bence-Jones proteinuria instead of albumosuria

The protein is found in 80% of the primary multiple myeloma, hardly ever in metastatic bone tumors (Naunyn, Marcovici). The absence of the protein in cases of primary multiple myeloma, is mentioned by Scheele and Herxheimer, Collins, Wallgren (7 cases), while the presence is cited by Bradshaw (one year before the appearance of the tumors (an amount of 13.9 gr per day), Oftedal, Cathcart (15 to 20 gr per day), Groves (63 gr per day), Auerbach Sexsmith, Henderson (15 to 20 gr)

Askanazy, Donetti, McCallum, McConnell, Buchstab and Schaposchnikow, Horsfall, Jochmann, Kimmerle (3 to 5%), Kahn in 2 cases, Wallgren (42 of the 118 cases in the literature, up to 1920)

The eliminated quantity reaches in some cases 70 gr per day, the amount decreases or can disappear entirely toward the end of the patient's life. The substance may derive from the tumors or through their damaging influence on the remaining marrow. The detection of the protein in the tumors or in the blood serum has been negative in the literature as reported by Hirschfeld. Since then, the pressure in the blood is mentioned by Jacobson, d'Alloco, Martini, in the spleen extract by Reach, in chloroma by Weinberger, in tuberculous osteoarthritis by Vidal, in myxedema by Jacksch, Fitz, in leukemia and in metastatic carcinoma by Boggs and Guthrie, in carcinoma ventriculi by Oerum, in ascite by Ellinger, in pneumonia sputum by Bradshaw, in bone marrow leukemia previously by Askanazy, in the pleural fluid by Goriat.

Decastello found serious changes in the kidneys accompanying the albu-

minuria (it is doubtful whether the kidney lesions are the primary moment allowing the passage of the protein, or the continuous passage of the protein damages the kidneys)

Massini finds that the amount of the excreted protein is equal to the amount of food protein taken.

(The reaction for the Bence Jones protein is very simple: the urine is tested for its acidity, acetic acid is added; if found neutral, then heated between 40° and 60° degrees C.)

A precipitate forms, which becomes soluble on further heating and reappears when getting cold. The substance gives all the color reactions for proteins.)

Up to 1914, 61 cases were reported by Kahn of true primary multiple myeloma, 70 cases with post mortem reports are accounted for by Kimmerle, Schumm and Fraenkel.

Martini's 206 cases may include some doubtful cases, since the very valuable contribution to the myeloma literature of Wallgren from 1920 reports only on 118 well studied cases followed by post mortem examinations.

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# Endocarditis Following Septic Abortion With Special Reference to Sub-Acute Bacterial Endocarditis\*

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**T**HAT endocarditis, particularly sub-acute bacterial endocarditis, may be a sequel of infections during or following pregnancy, has received comparatively little attention, although many have considered the hazards incident to a pregnancy complicating a previously existing endocarditis. Acute malignant bacterial endocarditis, occurring more or less incidentally as a part of puerperal sepsis, has been recognized, and instances of this sort are common in any large series of cases of puerperal infection. By presenting three new cases from the Department of Pathology of the University of Michigan, this paper will endeavor to show that not only is acute malignant endocarditis a dreaded complication of puerperal infection, but that months afterward a typical sub-acute bacterial endocarditis may furnish a fatal sequel to an infected abortion which has passed the stage of acute manifestation.

In considering acute malignant endocarditis the differentiations made by Libman (1) will be accepted. He divides bacterial endocarditis into

acute, sub-acute and chronic, considering the average course of sub-acute bacterial endocarditis as four to eighteen months, the acute cases being more fulminating. The infecting organism in acute endocarditis is usually streptococcus hemolyticus, although more rarely other organisms, such as staphylococcus, influenza bacillus, pneumococcus, etc., may be causative. The clinical course is that of a profound septicemia, with embolic phenomena as a prominent feature. Petechiae, sharp attacks of upper left quadrant pain, hematuria, etc., are seen. The physical findings on examinations vary somewhat according to the damaged valve. As pointed out by Libman (2), Herrick (3) and others, the process is particularly apt to attack a previously damaged valve. The following case is illustrative of this group.

*Case I* Mrs. E. I., age 25, entered the University Hospital on the Gynecology Service, December 23, 1924, complaining of fever and bleeding from the vagina. Four weeks previous to her admission she stated that she had inserted a catheter into the uterus in an effort to produce abortion. Following this she passed two large blood clots, but experienced no profuse bleeding. After this she felt well and was able to perform her housework for a period of two weeks. At

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this time she again passed blood clots and bled profusely from the vagina for four days. Then she had a chill with fever of about 104 degrees and nausea but no vomiting. In spite of the severity of her symptoms she did not go to bed, but continued with her household duties. Bleeding continued until her admission to the hospital.

At the age of 10 she had an illness which she characterized as "rheumatism," but she stated that her joints were never swollen or red. She had no pharyngitis, tonsillitis or quinzy. Her catamenial history was negative and her last menstrual period was two months previous to her admission to the hospital. She had been married five years. Her husband was living and well. One child was living and well. There had been two previous abortions, one following a fall and the other induced by a catheter.

Physical examination showed the heart to be of normal size. Heart sounds were regular and of good quality. The first heart sound was replaced by a rough, low pitched, systolic murmur, heard best at the apex. The murmur seemed to extend back into presystole.

The abdomen was slightly tense in the lower quadrants. There were no masses, areas of tenderness nor muscle spasm. The spleen was questionably palpable.

Vaginal examination showed a foul, brownish discharge. The cervix was large and soft, showing a bilateral laceration. The uterus and adnexa were not palpated.

No petechiae were noted. There was no clubbing of the nails. No edema was present.

At this time the urine showed albumin four plus, many granular and hyaline casts, and strong tests for acetone and diacetic acid. The blood showed a secondary anemia, and a white blood count of 13,900 with 68% polymorphonuclear leukocytes. Blood culture was positive for streptococcus hemolyticus.

The patient was transferred to the Medical Service. During her stay in the hospital she had a septic fever, with chills followed by rise in temperature to between 103° and 105° with correspondingly rapid pulse and respirations. Repeated blood cul-

tures were positive for streptococcus hemolyticus. Four days following admission she developed a right panophthalmitis and a bilateral acute arthritis of the wrists. She gradually became weaker, sank into a stupor and died on December 29, six days after admission.

#### CONDENSED AUTOPSY PROTOCOL

Autopsy 97-AC. Prosectors: Drs. Simpson and Breakey. On external examination the body was seen to be that of a somewhat poorly nourished, but not emaciated woman of average build. Over the face were scattered pustules. The right eye showed purulent exudate covering the conjunctiva, with a clouding of the cornea so that the pupil could not be seen. The left eye was negative. Over the sacrum there was an area of decubitus measuring 5 x 4½ cm, appearing relatively fresh and covered by a dry reddish-brown crust. Herpes labialis was noted. There were no petechiae.

Examination of the brain showed no meningitis, but there was edema and congestion of the leptomeninges. The brain substance showed increased bleeding points and involving the left thalamus and part of the lentiform and striate nuclei was an area of softening measuring 2 x 2 cm.

On making the main incision 75 to 100 cc of thick fibrinopurulent exudate was found free in the peritoneal cavity. The pleural cavities contained no free fluid, but the pericardial sac contained about 40 cc of thick purulent material. The heart was about the size of the cadaver's right fist. There was purulent exudate with some fibrin over the external surface. In the myocardium there could be seen pale localized areas appearing grossly as anemic infarcts, varying from 0.5 to 1 cm in diameter. On opening the heart vegetations which had the appearance of being recent were seen on all the cusps of the aortic valve. Both flaps of the mitral showed vegetations, which appeared somewhat older, along their free edges and around the attachment of the chordae tendineae. The valve flaps were definitely thicker than normal, apparently due to an older healed inflammatory process.

The lungs were similar to each other and both showed an acute congestion. No infarcts were found.

On examination of the abdominal organs, the spleen was found to be about twice normal size. The capsule was smooth and had a reddish-blue color. Three anemic infarcts were present, one of which appeared to be infected. The splenic pulp was congested, and the Malpighian corpuscles were not readily seen. The gastrointestinal tract showed a fibrino-purulent exudate over the serosa. In the upper portion of the caecum there was a patch measuring 6 to 8 cm. in length where there was a diphtheritic membrane replacing the mucosa in an irregular pattern. The lymphoid tissue was hyperplastic throughout. A fibrino-purulent peritonitis was also present over the liver, which showed in addition considerable fatty change. The left kidney showed recent anemic infarcts. The parenchyma showed cloudy swelling.

The external genitalia were negative except for a thin leukorrheal discharge. The uterus was enlarged and soft. The tip of the finger could be inserted into the external os. There was a slight bilateral laceration of the cervix and slight eversion. The endometrium was bluish-red in color and in the fundus midway between the orifices of the Fallopian tubes was a mass measuring  $3 \times 1 \times \frac{1}{2}$  cm., which had the appearance of retained, necrotic placenta. The uterine cavity was covered by a blood-stained fibrinous exudate. One tube was tightly adherent to the posterior surface of the uterus. One ovary showed a large corpus hemorrhagicum.

#### MICROSCOPIC EXAMINATION DR. WARTHIN

*Heart* Active streptococcus endocarditis on an older thickened endocardium. Streptococcus abscesses in myocardium. Older areas of fibrosis in myocardium. Marked fatty degenerative infiltration, both subepicardial and subendocardial. Localized acute fibrino-purulent epicarditis over abscess in the myocardium. Abscess in subepicardial fat. Marked tiger heart.

*Uterus* Infected placental site. Necrotic

decidua. Diffuse diphtheritic endometritis. Streptococcus infection following abortion.

*Fallopian Tubes* One shows an acute perisalpingitis with plications infiltrated with polymorphonuclear leukocytes. Other tube practically normal.

*Vagina* Acute vaginitis.

*Pathological Diagnosis* Streptococcus septicopyaemia (following self-induced infected abortion). Diphtheritic endometritis. Acute purulent salpingitis. Generalized fibrino-purulent peritonitis. Acute mitral and aortic thrombo-endocarditis. Multiple streptococcus emboli with recent infected infarcts in spleen, kidneys, myocardium and brain. Localized acute purulent meningitis and pericarditis. Right-sided purulent panophthalmitis. Acute diphtheritic colitis. Pyoderma of face. Herpes simplex labialis. Acute passive congestion and parenchymatous degeneration of all organs. Tiger heart. Old appendectomy scar. Decubitus.

Cases similar to this are numerous in the literature. Westphal (4) reported such a case in 1861, and in 1872 Virchow (5) reported a series of such cases, and pointed out the importance of endocarditis as a phase of puerperal sepsis. Recently, Mathias and Pietrusky (6) in analyzing 55 cases from the Pathological Institute at Breslau found 7 cases of fresh endocarditis. The illustrative case cited has all the clinical features of an acute endocarditis. The source of the infection is readily discernible, as is usual in acute endocarditis. The rapid course, blood cultures positive for streptococcus hemolyticus and embolic phenomena, are all typical. The necropsy findings were characteristic.

throughout and established the connection between the infected abortion and the endocarditis

Sub-acute bacterial endocarditis shows a definite clinical difference from the acute type. The onset is characteristically insidious as compared to the more sudden onset of acute endocarditis. A general malaise, weakness, and lack of tone are usually the first symptoms. At this time there is usually an irregular fever, and often chills, but the patient is often able to perform her duties. What might be characterized as the terminal stage of the disease may be ushered in by embolic phenomena, and these are nearly always present at some time before death. Particularly are petechial hemorrhages usually seen at some period during the patient's illness. Blood cultures are frequently positive, although cases are reported with a typical clinical course and characteristic necropsy findings where the blood culture has been consistently negative. The course of the disease has generally been considered to be progressively fatal although Libman (7) has reported clinically cured cases. The duration varies from six weeks up to two or three years in exceptional cases. Often there are periods of recession of the disease followed by relapses, although the condition may be steadily progressive. The following two cases are submitted as typical sub-acute bacterial endocarditis following infected abortion.

*Case II* Mrs. M. C., age 19, entered the Internal Medicine Service of the University Hospital September 14, 1919, complaining of weakness and loss of weight. She was married and had one child 15 months old. As

a child she had measles and chicken-pox with good recovery. At the age of 12 she had typhoid fever, and stated that she was very ill for several weeks. Since that time she had enjoyed good health until the onset of the illness which caused her to come to the hospital. Her health since marriage had been as good as previously.

In February, 1919, she was pregnant about two months. Following the advice of a neighbor, she induced an abortion by passing a catheter, which she had made no attempt to sterilize, into the uterus. The abortion followed three days after the instrumentation. At this time she felt "sick at her stomach," and for a period of two weeks she had fever and several chills. She had never felt well since that time. There was a thick yellowish discharge from the vagina, but she experienced no pain except for painful urination for a short time. She had noticed loss of weight, although she did not know how much, and said her heart pounded and was irregular. These symptoms increased and she became weaker until finally she consulted a physician, about August 1, who put her on a liquid diet. She followed this treatment at home for three weeks and then entered a hospital in another city where she remained twenty days, steadily growing worse. At the end of that time she came to this hospital.

Physical examination showed a small woman of anemic appearance, with a faint flush over the cheeks and a slight cyanosis of the lips. The nodes of the posterior cervical chain were slightly enlarged and tender. There was a bounding pulsation of the great vessels of the neck with definite venous pulse.

Examination of the heart showed the apex beat to be visible in the precordium. The cardiac rhythm was regular but rapid. The first sound at the apex was ringing and accompanied by a soft systolic murmur. Immediately following the first sound and replacing the second sound was a loud blowing diastolic murmur lasting throughout diastole and well transmitted to the axilla. Over the aortic area there was a loud murmur lasting throughout systole and diastole.

ately followed by an equally loud murmur lasting throughout diastole

Examination of the lungs show impairment of percussion resonance at both bases. Breath sounds in these regions were faint and distant, and deep inspiration brought out a coarse friction sound. Examination of the abdomen was negative. Neither liver nor spleen could be felt. The fingers showed clubbing and curving of the nails. There was no edema of the extremities. No petechiae were seen.

During her stay in the hospital, she had a rise in temperature every afternoon. Six days after admission the patient complained of pain over the heart and experienced difficulty in breathing. The next day she was drowsy and during the afternoon she had the usual rise in temperature, became restless, and the pulse became more rapid. The next morning she was dyspneic, cyanotic, and showed a very slow labored pulse. Respirations gradually became slower and more labored, and she died quietly at 6 55 A.M. September 22, eight days after entering the hospital.

#### CONDENSED AUTOPSY PROTOCOL

Autopsy 26-X. Prosector Dr. Weller. The body was that of a young adult female of slight build, showing fair nutrition, but marked pallor. The main incision showed no free fluid in either abdomen or chest.

The heart was markedly enlarged and showed no evidence of pericarditis. On opening the heart, the mitral cusps were seen to be beaded with organized and ulcerated vegetations. In the right cusp there was an aneurysm measuring 5 mm in diameter. All the cusps of the aortic valve showed an extreme degree of ulceration, one being eroded until only about 3 mm remained. From the edges of this extended stringy masses of fibrin. These vegetations extended up into the first portion of the aorta.

The lungs showed congestion but there was no consolidation. The abdominal examination showed a spleen four times normal size. The splenic pulp was hyperplastic, and there was marked congestion. There was one small anemic infarct measuring 3 x 5 mm. The kidneys were slightly

larger than normal. There was well marked cloudy swelling, and in the left kidney a small area of partly healed anemic infarction. Otherwise the abdominal examination revealed nothing of interest.

Coming from the vulva was an abundant purulent discharge, smears of which showed streptococci and bacilli. There was a small amount of exudate over the endometrium, but no severe process. The uterus was of about normal size. Ovaries were normal in size and showed no large corpora lutea.

#### MICROSCOPIC EXAMINATION DR. WARTHIN

*Heart* Fatty infiltration with serous atrophy. Marked atrophy and fatty degenerative infiltration of heart muscle. Organizing vegetations. Sub-acute endocarditis.

*Spleen* Marked chronic passive congestion. Lymphoid atrophy. Exhaustion of germ centers.

*Kidneys* Cloudy swelling. Atrophy. Congestion. Serous atrophy of the subpericardial fat. Areas of chronic inflammation. Fresh anemic infarcts.

*Uterus* Endometrium atrophic. Small leiomyofibroma.

*Ovaries* Chronic ovaritis and periovaritis. Imperfectly resolved corpora fibrosa with calcification.

*Tubes* Negative.

*Pathological Diagnosis* Sub-acute thrombo-endocarditis of mitral valve with valvular aneurysm. Ulcerative endocarditis of aortic valve. Aortic stenosis and insufficiency. Cardiac dilatation and hypertrophy. Anemic infarction of spleen and kidney. Severe secondary anemia. Serous atrophy of fat tissue. Marked fatty heart. Tiger heart. Passive congestion and parenchymatous degeneration of all organs. Streptococcus septicæmia (post-abortion).

*Case III* Mrs. E. O., American housewife, of 18 years, entered the Neurological Service of the University Hospital on the

t of November, 1927, complaining of paresthesia of the left side of the body, pain in the right calf, and general malaise and weakness.

The patient was married at 13. She had a child 3 years old, living and well. She had about seven self-induced abortions, the last one in July, 1927, when she was about 4 months pregnant. She was taken to a hospital at that time. Ever since that time she felt below par, although she had definite symptoms with the exception of foul discharge from the vagina. About two weeks before entrance, after pumping a pail of water and walking back to the kitchen, it was noticed that the right side of her face was pulled out of shape. The left arm and leg became paralyzed and she was unable to walk. She was not unconscious. She was again in the hospital a short time and partially regained the use of her left leg. The left arm and the side of her face remained paralyzed.

Physical examination disclosed a well-nourished and well-developed young woman of poor mentality who cooperated fairly well. She did not, however, know her age exactly. Examination revealed a hemiplegia, most marked in the face and arm, the patient having partial use of the left leg sufficient to enable her to stand and walk easily. The heart was slightly enlarged on percussion. There was a systolic murmur heard over the aortic area which was of a soft character and a very faint diastolic murmur. The pulse was of the irregular type, the blood pressure 135/20. The liver and spleen could not be palpated. There was no use of voluntary abdominal rigidity. On pelvic examination revealed retroversion of the uterus, which was enlarged and boggy. There was a brownish discharge which was

bloody. Wassermann was negative. On the blood culture showed Gram positive cocci, probably streptococcus viridans. The sediment showed a moderate amount of albumin, hyaline and granular casts, occasional red blood cells and many white blood cells. The blood showed hemoglobin, 50%, red blood cells, 2,500,000, white blood cells, 10,000, differential — polymorphonuclears,

73%, lymphocytes, 13%, endotheliocytes, 8%. The electrocardiogram showed marked sinus tachycardia, but was otherwise normal. The X-ray on November 23rd showed cardiac enlargement, flattening of the left auricular curve, and clear lung fields.

The temperature fluctuated from 100° to 102°. During the latter part of her stay in the hospital her pulse averaged about 130, respirations, 40 to 68. On November 29th, the lungs, which had previously been clear, revealed râles and bronchial breathing in the lower right chest and a somewhat more marked involvement of the left. The liver at this time was palpated one hand's breadth below the costal margin. Her symptoms became progressively worse and she died December 1st.

#### CONDENSED AUTOPSY PROTOCOL

Autopsy 103-AF. Prosectors: Drs. Well-er and Fortune. The body was that of a well developed young adult female, showing no evidence of loss of weight. The skin had a noticeably gray tinge. There was a lack of tone in the muscles of the left side of the body. Rigor mortis had not set in. Edema was present in both ankles, but more marked on the left.

In the right temporal lobe there was an area of softening measuring 5 x 5 x 5 cm, extending back into the basal ganglia, giving an area of softening in the floor of the right lateral ventricle. The right cerebral peduncle also showed an area of softening.

The heart was much larger than the cadaver's right fist, measuring 12 x 10 x 5 cm, and weighing 410 gms. There was a small soldier's spot on the anterior surface of the right ventricle and on the posterior aspect of the left ventricle there was a sharply localized area of adhesion between the parietal and visceral pericardium. On opening the heart there were many ulcerating vegetations seen extending along the edge of the aortic flap of the mitral valve for a distance of one centimeter. One centimeter above this line of vegetation there was a nipple-like projection 5 mm in its diameter extending into the left auricle. On investigation from below this was seen to be an aneurysm of the flap. Just below

the cusps of the aortic valve were numerous vegetations, completely surrounding the orifice and extending up onto the cusps. This process was much more marked than on the mitral valve. In the right ventricle on the septum, just opposite the mass of vegetations described below the aortic valve, there was a projecting mass of vegetations, which proved to be a mycotic aneurysm extending through the septum from the left heart. This aneurysm involved the flap of the tricuspid valve adjacent

The lungs showed a brownish color, but not the firmness of induration. There was a marked congestion. Both lungs contained hemorrhagic infarcts, the largest of which was in the lower lobe of the right lung, and had a base 8 cm in diameter with a fibrin-

nous pleuritis over the surface. The pulmonary vessels contained thrombi, some of them old and yellowish-white in color. On section of the spleen numerous small subcapsular infarcts were seen. The kidneys showed both old healed infarcts and more recent infarcts, some of them very fresh.

The cervix uteri showed a large polypoid mass projecting through the external os. The upper attachment of this mass was in the uterine cavity at the right upper pole. This was covered by purulent exudate and had the appearance of an infected fleshy mole. The endometrium was hyperplastic and congested. The left ovary showed a large corpus luteum. The tubes appeared negative except for congestion.

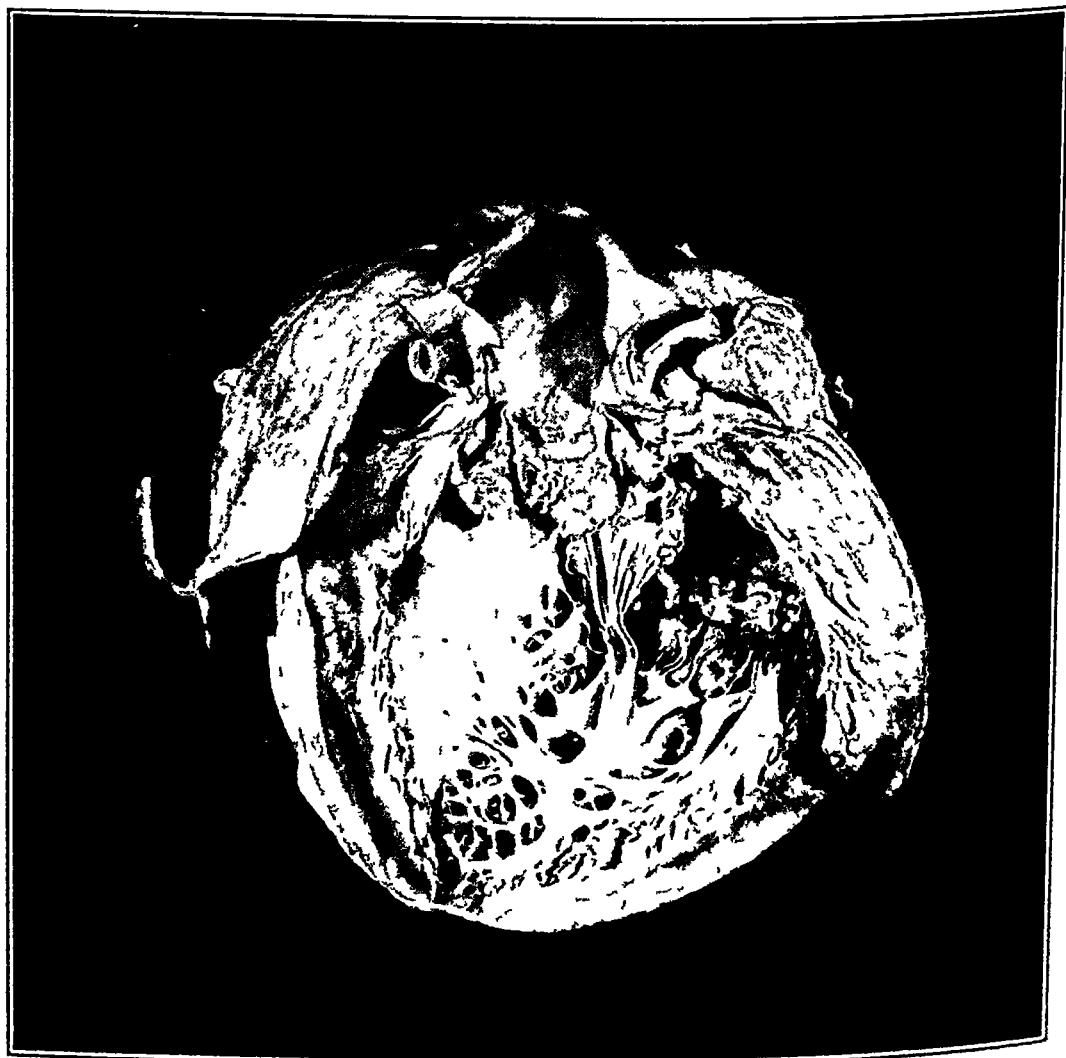


FIG 1 Heart from Case III, showing vegetations on the aortic valve

## MICROSCOPIC EXAMINATION DR WARTHIN

*Brain and Meninges* Marked congestion and edema. Localized meningeal reaction over the areas of softening. Multiple large areas of anemic softening scattered throughout the brain, in both cerebrum and cerebellum. Most of these are very recent as there is very little proliferation about the borders. No sclerosis of meningeal or cerebral arteries.

*Heart* Subepicardial fatty infiltration. Diffuse fatty degenerative infiltration, most marked under the endocardium. Extreme tiger heart. Muscle fibers are atrophic. Subacute bacterial endocarditis, still in active stage. Sclerosis of endocardium, with fresh vegetations on surface containing large bacterial colonies. At the base of these vegetations small tears extend through the thickened inflamed endocardium—first stage of aneurysm formation. Coronaries show slight lipoidosis of intima. No areas of either active or healed myocarditis.

*Lungs* Extreme congestion and edema. Multiple thrombosis of pulmonary veins. Multiple hemorrhagic infarctions. Extreme edema. Numerous pigmented "Herzfehler" cells but no induration of lungs. Areas of marked atelectasis with acute purulent bronchitis and beginning broncho-pneumonia. Fat stains show no fat emboli.

*Spleen* Extreme congestion. Multiple infected anemic infarcts. Infected emboli. Marked necrosis of the splenic follicles.

*Kidneys* Congestion. Atrophy. Slight cloudy swelling. Very few scarred glomeruli, except in areas of healed infarcts. Multiple anemic infarctions in all stages, some wholly recent, others healing. Fat stains show practically no lipoidosis.

*Cervix of Uterus* Severe glandular erosion. Chronic catarrh.

*Body of Uterus* Localized polypoid cystic glandular hyperplasia. Extreme congestion. Some blood pigment. Vessels show resolution—post pregnancy. Incomplete resolution. Cavity of uterus filled with a fleshy mole containing necrotic and still living chorionic villi decidua and infected blood clots. Infected retained placenta fol-

lowing abortion. In the uterine and vaginal plexus there are infected thrombi.

*Ovaries* Unresolved corpus luteum. A few cystic follicles.

*Tubes* Subacute inflammation.

*Pathological Diagnosis* Septicopyaemia (streptococcus). Retained infected abortion. Sub-acute septic vegetative endocarditis involving aortic and mitral flaps. Valvular aneurysm of mitral cusp. Mycotic aneurysm between root of aorta and right ventricle. Multiple embolic infarcts of brain, spleen, kidneys, lungs and abdominal wall. Early pyaemic abscess formation. Marked fatty degenerative infiltration of heart muscle. Extreme nutmeg liver. Marked passive congestion of all organs. Simple colloid goiter.

## DISCUSSION

In both of these cases it will be noted that from a clinical point of view the onset was insidious and not accompanied by characteristic symptoms. This period preceding the onset of serious symptoms was long in one case six months in the other case more than four months. In Case III brain embolism initiated the final stage of the disease in Case II there were simply increasing weakness and disability. Unfortunately no blood culture is recorded for Case II. In Case III streptococcus viridans was present intra vitam and a blood culture was taken from the heart post mortem and showed also characteristic streptococcus viridans. Both cases showed during their stay in the hospital the usual findings of a septic endocarditis.

Pathologically all three cases are typical vegetative thrombo-endocarditis. It will be noted that there is no characteristic difference post mortem between acute malignant endocarditis and sub-acute bacterial endocarditis, except for the fact that in the case of sub-acute bacterial endocarditis the heart lesions are, as the name implies, in the sub-acute stage and some of the embolic lesions are generally in the healing stage. In Cases I and III the infective process was still active in the uterus, in Case II this had subsided to a considerable degree. However, the exudate from the uterus and vulva still showed streptococci, and with the clear clinical history connecting the endocarditis with the abortion, there seems no question but that it should be considered as a sequel of a postabortal sepsis. In the acute case it will be noted that there was a generalized peritonitis which might well be considered as a direct extension from the uterus. In the sub-acute cases, however, the secondary foci of infection were all such as might well be attributed to the heart lesion. In other words, the endocarditis was apparently the only process of infection resulting from the puerperal sepsis and the lesions throughout the body were secondary to the process in the heart. Without an association of the clinical and necropsy findings, the connection between the abortion and the endocarditis might well be missed in such cases.

Pathologically Cases II and III are interesting quite aside from the connection between the abortion and the endocarditis. Both cases showed involvement of the mitral valve. In

Case III there was in addition to this a mycotic aneurysm at the base of the aortic valve extending through into the right ventricle, involving the tricuspid valve. Mycotic aneurysms are not unusual in bacterial endocarditis, but it is rare to have the tricuspid valve involved by vegetative endocarditis, and still more rare to have it involved by an aneurysm arising on the other side of the heart and passing through the septum. The presence of these vegetations in the right side of the heart explains the occurrence of the hemorrhagic infarctions in the lung found in this case.

These three cases call attention to the fact that endocarditis, whether acute or sub-acute, is pathologically the same condition, the variation in the clinical picture being largely dependent upon the virulence of the infecting organism. The fact that bacterial endocarditis is particularly prone to attack a previously damaged valve, has been emphasized by Libman (2), Herrick (3) and others. In one of the cases presented, there was a healed endocarditis of the valve which preceded the more recent process. In another there was sclerosis of the endocardium, which may have indicated an older endocarditis. It has been generally accepted that in sub-acute bacterial endocarditis the source of infection is not apparent and such "foci of infection" as tonsils, teeth, etc., have been given prominence as source of entry for the infecting organism. The question may well be raised whether in many of the cases the element of time has not obscured an evident source of infection. For example in a case of septic abortion



following the infection in the uterus there is entrance of organisms into the blood stream. If one of the valves of the heart has been damaged by a previous endocarditis, there is a locus of lowered resistance at which the organisms may settle out. If the infection is with streptococcus hemolyticus, the patient may have a typical acute endocarditis septicaemia, if it is streptococcus viridans she may six months later develop a sub-acute bacterial endocarditis, which neither pathologist nor clinician may associate with the abortion.

No attempt is made to assert on the basis of such a small number of cases, what is the frequency with which sub-acute bacterial endocarditis follows an infection of pregnancy. Neither is there any attempt to refute any established beliefs concerning the origin of the infection in other cases of bacterial endocarditis. However, with these cases in which the connection seems well established, and recognizing the pathological similarity of the sub-acute forms to the acute forms, it seems justifiable to call attention to the possibility that sub-acute, as well as acute bacterial endocarditis, may be a frequent complication of puerperal sepsis. If this be so the careful internist in investigating a case of sub-acute bacterial endocarditis occurring in a woman of child-bearing age, must consider the possibility of an infection of pregnancy as a possible source for the infecting organisms of the endocarditis. Furthermore the obstetrician who has a case of puerperal infection or infected abortion under his care must

bear in mind the possibility that even though the acute manifestations of the disease are successfully passed, there is still the possibility that an endocardial involvement may occur at a later period. The instances cited emphasize the danger of an untreated septic abortion since all the cases of endocarditis following abortions which have come to our attention had received no medical treatment until the sepsis was well established. It seems quite possible that thorough and prompt removal of the infected focus in the uterus might prevent such cases of delayed endocarditis and even perhaps the cases of more acute endocarditis.

#### SUMMARY

Three additional cases of bacterial endocarditis resulting from uterine infection following abortion are presented. Attention is called to the well-established fact that an acute endocarditis is a frequent and serious complication of puerperal sepsis. One of the cases presented is illustrative of this type of cardiac disease. Sub-acute bacterial endocarditis, while differing clinically in its course, is recognizable as being the same pathological process, differing only in stage, the clinical peculiarities being due probably to the type of infecting organism. The other cases illustrate the fact that sub-acute, as well as acute, bacterial endocarditis may be a complication of infection following abortion. In these instances the cardiac condition dominates the clinical picture and the connection with the previous abortion is easily overlooked.

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# Familial Glycosuria. Report of a Large Family.

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THE familial occurrence of glycosuria is attracting increasing interest and families displaying this symptom in several members deserve special study. Joslin (1) records a family in which twelve brothers and sisters, and two children are thought to have had diabetes. He reports a Jewish family, eight members of which had diabetes. Landis (2) reports a diabetic family in which the disease was present in the five blonde but not in the four brunette children of a diabetic mother. These are striking examples of families in which all of the individuals showing glycosuria are sufferers from diabetes.

Additional large families have been studied in which non-diabetic as well as diabetic glycosuria has been present in several members.\* Holst (3) gives a good bibliography of the Scandinavian literature and reports eleven families in which two or more members displayed glycosuria, the largest number of glycosuric members in a family was eight. The largest number of diabetics in any of these families was four, the remaining members showed a benign glycosuria. In each of ten of these families the

blood sugar reaction of one member was studied after the administration of glucose, two members of the eleventh family were studied in this manner. Hatlehol (4) reports twelve families, members of which showed benign glycosuria, diabetes was present in five of these families. Malmros (5) reports a family in which 12 members showed glycosuria in the absence of any symptoms of disease.

The following report is concerned with the study of a family in which eighteen members show the presence of a reducing substance in the urine in the absence of any symptom of diabetes. Figure I shows the family tree, designating the affected members. In five members the blood sugar response to glucose administration by mouth has been studied, the resulting curves display, in one case, the reaction characteristic of mild diabetes mellitus, in two cases the result is typical of renal glycosuria, in two cases of cyclic renal glycosuria, and in thirteen members the type of blood sugar response has not been studied.

The urine specimens from those members of the family whose responses to glucose have not been studied were collected about two hours after the largest meal of the day because such postprandial specimens are the ones most likely to contain glucose.

\*Hjärne (*Acta Med Scandinav* 67, p. 422, quoted by Malmros) studied 109 members of a family and found glycosuria in 41 members.

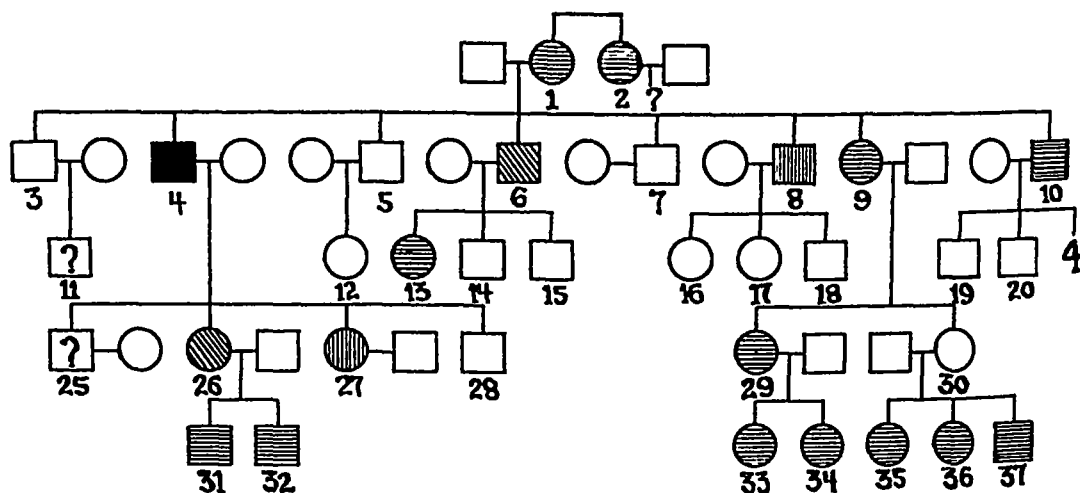


CHART I Family tree Legend The square symbols represent males, the circular symbols represent females The numbers under each symbol correspond to the member number in the text Solid black represents diabetes, diagonal hatching represents renal glycosuria, vertical hatching represents cyclic renal glycosuria, horizontal hatching represents glycosuria of an undetermined type, the urine of members represented by plain symbols did not contain glucose The urine of those designated by an interrogation mark has not been tested

The three types of glycosuria mentioned above have the following characteristics—The mild diabetic (6) displays a fasting blood sugar slightly above the normal, accompanied by the presence or absence of sugar in the simultaneous urine specimen. Following the administration of glucose by mouth, the blood sugar rises to an abnormally high level, usually reaching the peak of the rise only after an hour's time, accompanied by the appearance of sugar in the urine. The blood sugar level then decreases slowly and is still above normal at the end of three hours.

With renal glycosuria, the fasting blood sugar level is normal or low, and the simultaneously voided urine contains sugar. Following the administration of glucose by mouth, the blood sugar level does not as a rule rise even as high as in the normal individual, the peak of the rise is usually

reached within forty minutes and within two hours the blood sugar has returned to a normal level. Varying quantities of sugar are excreted in the urine throughout the test.

With cyclic renal glycosuria (7), (8) the fasting blood sugar level is normal and the simultaneously voided urine is sugar-free. Following the administration of glucose by mouth, a curve similar to the normal blood sugar response is observed. Accompanying the normal rise in the blood sugar, the simultaneous urine specimens begin to contain sugar at a blood sugar level, usually between 120 and 140 milligrams per 100 cc of blood, demonstrating a low renal threshold for glucose. In other words, glucose appears in the urine only after the ingestion of food or glucose, while in renal glycosuria the urine usually does not become sugar-free even during periods of fasting.

# REPORT OF FAMILY

The urine specimens from thirteen glycosuric members of the family have been studied by the author, who is indebted to D<sup>r</sup> J L Porter for his assistance in discovering glycosuria in several of the members studied Dr N Peterson and Dr J B H Day determined the presence of a reducing substance in the postprandial urine of other members of the family It is unfortunate that some members could not be located, and that two declined to submit specimens for examinations

*Member 1* White female, aged 78, has been obese but is now thin A recent specimen of urine contained a large amount of reducing substance

*Member 2* White female, aged 70, a sister of member 1, is said to be thin A recent urine examination showed a trace of reducing substance

*Member 4* White male, aged 56, a son of member 1, was seen April 13, 1927 His past history was unimportant except for frequent attacks of epigastric pain as a young man, these attacks had occasionally required a hypodermic of morphine for relief He had passed his urine one to three times during the night for fifteen years, but had had no other symptoms of diabetes He had never weighed more than 145 pounds (65.9 Kg) until he stopped smoking during 1919, following this he had gained weight rapidly and had reached his greatest weight of 207 pounds (94.0 Kg) one month ago He had exhibited a slight elevation of blood pressure Sugar had been discovered in his urine during a life insurance examination in 1923 He had not followed a diet and occasional subsequent urine examinations had always shown sugar His height was 5 feet 6 inches (167.6 cm) and his naked weight was 196 pounds (89.1 Kg) Table 1 shows his blood and urine response to glucose displaying the type of reaction observed in the mild diabetic

*Member 6* White male, aged 36, a son of member 1, was seen Jan 1, 1927 His past history was unimportant Starting three years ago he had had nycturia one to three times, some polyuria and marked urgency, during the past year he had not had to pass his urine during the night He had had no other symptoms of diabetes Sugar had been discovered in his urine during a life insurance examination in 1916, at which time he had weighed about 150 pounds (68.2 Kg) Later, the sugar had disappeared and he had been able to obtain insurance His urine has continued to show sugar at times His greatest weight had been 175 pounds (80.0 Kg), two years ago, his average weight was 160 pounds (72.7 Kg) His height was 5 feet 8¾ inches (174.6 cm) and his naked weight was 155 pounds (70.5 Kg) Table 1 shows his blood sugar curve and urine findings after glucose The type of response is characteristic of renal glycosuria, although the history of becoming sugar-free at times, suggests cyclic renal glycosuria

*Member 8* White male, aged 43, a son of member 1, was examined Nov 24, 1926 His past history was unimportant He had been rejected for life insurance during 1916 because of sugar in his urine, at which time he had weighed about 170 pounds (77.3 Kg) He had restricted carbohydrates for six months following this experience and had then been accepted for insurance There had been no subsequent urine examination He had passed his urine once or twice during the night for about 10 years, but had had no other symptoms of diabetes His average weight was 180 pounds (81.4 Kg) and his greatest weight had been 190 pounds (86.4 Kg) one year ago His height was 5 feet 9½ inches (176.5 cm), and his naked weight was 178 pounds (80.9 Kg) Table 1 shows the blood sugar and urine findings after glucose the type of reaction is characteristic of the condition described as cyclic renal glycosuria

*Member 9* White female, a daughter of member 1, is said to be very obese A recent urine examination showed the presence of a small amount of reducing substance

TABLE I—GLUCOSE TOLERANCE TEST

Member Number	Member 4			Member 6			Member 8	
	Blood Sugar in mg per 100 c c	Urine Volume	Urine Sugar	Blood Sugar in mg per 100 c c	Urine Volume	Urine Sugar	Blood Sugar in mg per 100 c c	Urine Sugar in grams
Fasting	122	50 c c	0	87	20 c c	Trace	105	0

100 grams glucose as lemonade

30 min after glucose	200	25 c c	0.3%	133	70 c c	0.8%	171	0.9
1 hour after glucose	250	50 c c	1.3%	111	200 c c	0.3%	135	6.0
2 hours after glucose	190	200 c c	0.8%	99	170 c c	Trace	107	1.2
3 hours after glucose	124	60 c c	0.1%					

*Member 10* White male, aged 60, a son of member 1, weighs 210 pounds (95.5 Kg) and is 5 feet 8 inches (172.7 cm) tall, a reducing substance has been found in his urine by several physicians over a period of years

*Member 13* White female, aged 13, a daughter of member 6, and a granddaughter of member 1, has a small amount of reducing substance in her urine after a meal

*Member 26* White female, aged 21, a daughter of member 4, and a granddaughter of member 1, was seen Feb. 4, 1925, during the early weeks of her second pregnancy. Sugar had first been found in her urine during the early weeks of her first pregnancy, Oct. 21, 1922, starvation for three days and subsequent restriction of diet had not rendered the urine sugar-free. Her greatest weight had been 115 pounds (52.6 Kg) during 1922. Her average weight was 107 pounds (48.6 Kg). She had never had any symptoms of diabetes. Her height was 5 feet 2 inches (157.5 cm) and her naked weight was 101 pounds (45.8 Kg). The blood and urine response to glucose, determined March 6, 1925, is shown in Table 2, taken from a report of respiration studies of renal glycosuria by Paullin (9). During the remainder of the second pregnancy, the puerperium, nursing period and subsequently, this patient's glucose excretion was studied and reported by Bowcock and Greene (10). On Nov. 7, 1928, a 24 hour specimen of urine, volume 1200 cc., contained 35 grams of glucose. This patient writes that she is in good health and weighs 109 pounds (50.0 Kg).

*Member 27* White female, aged 28, a daughter of member 4, and a granddaughter of member 1, was seen Nov. 7, 1928. The past history was unimportant. She had had no symptoms of diabetes and had had nycturia only during her menstrual periods. Her greatest weight had been 125 pounds (56.8 Kg) 10 years ago, her average weight was 105 pounds (47.7 Kg). I had found 0.1 per cent sugar in a single specimen of urine during November 1926. During June 1927 I examined urine passed two hours after a large meal. This specimen contained 3.0 per cent sugar. The urine was dextro-

rotary in the polaroscope and was fermented by yeast. Her height was 4 feet 10 inches (147.3 cm) and her naked weight was 100 pounds (45.5 Kg). Table 3 shows the blood and urine response characteristic of cyclic renal glycosuria following the ingestion of glucose.

*Member 29* White female, aged 33, is a daughter of member 9, and a granddaughter of member 1. Her height is 5 feet 2 inches (157.5 cm) and her weight is 158 pounds (71.8 Kg). On Nov. 17, 1928, a specimen of urine passed after a meal contained a small amount of reducing substance. On Nov. 25, 1928, a postprandial specimen contained 0.43 per cent glucose. The reducing substance reduced Benedict's and Nylander's solutions and gave a heavy yield of osazone crystals with phenylhydrazine.

*Member 31* White male, aged 5 years, 6 mos., a son of member 26, and a great grandson of member 1, weighed 6 pounds 4 ounces at birth (2.8 Kg). When one year ten months old, I examined a specimen of his urine which contained 0.1 per cent dextrorotary reducing substance, three subsequent examinations showed a trace of reducing substance on one occasion, and none at the other examinations. On Nov. 9, 1928 he was 3 feet 7½ inches (115 Kg) tall, and weighed 45 pounds (20.5 Kg). A specimen of urine collected two hours after a meal contained 0.23 per cent sugar. The urine gave reduction of Benedict's and Nylander's reagents and yielded an osazone with phenylhydrazine. This child is in good health.

*Member 32* White male, aged 3 years 2 mos., a son of member 26, and a great grandson of member 1, weighed 7 pounds (3.2 Kg) at birth. Except for a mild degree of rickets he has had good health. A specimen of urine at the age of four months gave no reduction of Benedict's solution. On Nov. 9, 1928 his height was 3 feet ½ inch (92.7 cm) and his weight was 33 pounds (15.0 Kg). A specimen of urine passed two hours after a meal gave slight but definite reduction of Benedict's and Nylander's solutions and a good yield

TABLE 2—RESPIRATION EXPERIMENTS\* MEMBER 26

	Respira- tory Quotient	Calories per Hour	Rise in Calories per Hour	Calories per Square Meter per Hour	Rise Above Normal, Per Cent	Calories from Carbo- hydrate and Fat	Calories from Carbo- hydrate, Per Cent	Calories from Carbohy- drate	Grams Carbohydrate		Blood Sugar, Mg per 100 Cc	Urine Sugar, Gm
									Utilized	Increase		
Basal	0.78	55.4		37.9	—2	47.1	26.3	12.3	3.0		78	+
79 Gm dextrose 45 minutes after	0.87	62.2	6.8	42.6	16.5	52.8	57.5	30.3	7.6	4.6	133	3.5
1½ hours	0.78	59.7	4.3	40.9	11.0	50.7	26.3	13.4	3.3	3	132	2.0
2½ hours	0.76	56	0.6	38.4	3.5	47.6	19.2	9.2	2.3	—7	100	1.5
Dextrose administration											79.0 Gm	
Dextrose excreted											7.0 Gm	
Dextrose metabolized, 10.5 Gm, 14.6 per cent of total											72.0 Gm	

\*Technic as described by Boothby and Sandiford, Tissot gasometer and Haldane gas analysis apparatus The results demonstrate normal utilization of dextrose



TABLE 3—GLUCOSE TOLERANCE TEST

Member 27	Blood Sugar in mg per 100 c c	Urine Volume	Urine Sugar
Fasting	89	15 c c	Negative
100 grams glucose as lemonade			
20 min after glucose	131	11 c c	1 Plus
40 min after glucose	134	45 c c	3 Plus
1 hour after glucose	122	75 c c	3 Plus
2 hours after glucose	105	445 c c	2 Plus
3 hours after glucose	83	220 c c	1 Plus
Total volume urine containing sugar		796 c c	0.38% = 3 gms

of osozone crystals when treated with phenylhydrazine

*Member 33* White female, aged 12, is a daughter of member 29, and a great granddaughter of member 1. Her height is 4 feet 8½ inches (143.5 cm) and her weight is 70 pounds (31.8 Kg). At two examinations postprandial specimens of urine have reduced Benedict's and Nylander's solutions and given a good yield of osozone crystals.

*Member 34* White female, aged 4, is a daughter of member 29, and a great granddaughter of member 1. Her height is 3 feet 2 inches (96.5 cm) and her weight is 30 pounds (13.6 Kg). On two occasions her postprandial urine has reduced Benedict's and Nylander's solutions, at one examination the quantitative reduction was 0.29 per cent. A heavy yield of crystals was obtained with phenylhydrazine.

*Member 35* White female, aged 7, is a daughter of aglycosuric member 30, (member 30, aged 25, is 5 feet 5½ inches tall and weighs 188½ pounds, a postprandial specimen did not reduce Benedict's solution), and a great granddaughter of member 1. Her height is 4 feet 3 inches (129.5 cm) and her weight is 52 pounds (23.6 Kg). One of two postprandial specimens gave slight reduction of Benedict's and

Nylander's solutions, and a good yield of osozone crystals.

*Member 36* White female, aged 5, a sister of member 35, is 3 feet 7 inches tall (109.2 cm) and weighs 39 pounds (17.7 Kg). Two postprandial urine specimens gave slight reduction of Benedict's and Nylander's solutions and a good yield of osozone crystals.

*Member 37* White female, aged 3, a sister of member 35, is 3 feet 2½ inches tall (97.8 cm) and weighs 35 pounds (15.9 Kg). Two postprandial specimens of urine produced definite reduction of Benedict's and Nylander's solutions and yielded osozone crystals after treatment with phenylhydrazine.

## DISCUSSION

In spite of the fact that only one or two postprandial urine specimens from most of the individual members of this family were examined positive reduction was obtained with the urine of eighteen members. This high percentage of positive results (58 per cent) suggests that had specimens been examined at more frequent in-

tervals the strong hereditary trend of this symptom, glycosuria, would have been evidenced by a still higher percentage of positive results

As far as could be determined, all members of the family are in comparatively good health, and in none have the classical symptoms of diabetes mellitus been present. The family is remarkable for the fact that it shows no member with typical symptomatic diabetes. The absence of such symptoms, however, does not exclude the presence of mild diabetes, and studies of the blood sugar response to glucose ingestion would probably demonstrate the presence of a mild diabetic type of reaction in some of the asymptomatic adult members besides member 4. The juvenile members have most probably a benign glycosuria. The types of blood sugar and urine response to the ingestion of glucose displayed by the members thus studied, comprise the usual types of reaction noted in such families. There is, in addition to such types, a rarer type of benign glycosuria which may be present in this family. Campbell (11) has described this rare type under the designation of diabetes innocens. The condition is characterized by a low renal threshold, giving rise to the presence of sugar in urine collected simultaneously with a low or normal fasting blood sugar. There are usually no symptoms of diabetes. After food the blood sugar does not exceed the normal postprandial level, while following the ingestion of glucose the blood sugar level increases to the point of a definite hyperglycemia but returns to normal within three hours. No special

dietary restriction is necessary for the well-being of such individuals. Vogelzang (12) has described two such cases which he classifies as a probable combination of diabetes mellitus and renal glycosuria. Parsons (13) has reported a similar case under the title of "benign glycosuria with hyperglycemia." Holst (14) mentions a further case. Malmros (15) records an example in one of the glycosuric families, and Paulin and Bowcock (16) have made a detailed study of a similar case with special threshold studies in a patient who was unaware of any other cases of glycosuria in his family.

Whether or not any of the members of this family will subsequently develop symptomatic diabetes is problematical. Holst (3) and many others are of the opinion that a transition from benign non-diabetic glycosuria to true diabetes seldom, if ever, occurs. Malmros (17) after studying the reaction of such glycosuric individuals to insulin and noting that although they developed hypoglycemic symptoms, they did not become sugar-free, concluded that an insufficiency of the pancreas does not cause these forms of glycosuria.

#### SUMMARY

A family is reported, eighteen members of which (representing 58 per cent of the members studied) displayed the presence of a reducing substance in the urine in the absence of other symptoms of diabetes. Glycosuria was first discovered at 22 months in the youngest, and at 78 years in the oldest member. The condition is present in four generations. The blood and urine

response to glucose ingestion has been determined in five members, showing the responses characteristic of mild

diabetes mellitus in one case, of cyclic renal glycosuria in two cases, and of renal glycosuria in two cases

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# A Study of Atrophic Cirrhosis of the Liver in Relationship to Syphilis\*

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**T**his paper comprises a review of all cases of cirrhosis of the liver which have occurred in the pathology service of the University of Michigan from the year 1895 through the major part of the year 1925, with the exception of all cases of central cirrhosis, biliary cirrhosis, fatty cirrhosis, and four cases that could not be definitely classified. Special emphasis is placed upon the concomitant presence of histological evidence of syphilis, either in the liver, or elsewhere in the body.

An exhaustive resumé of the literature was not attempted. Cirrhosis of the liver was described as a hardening of the liver by Vesalius (1514-1564), Harvey, and Morgagni (1). Payne's review (2) of the history of cirrhosis of the liver points out that the earlier workers attributed its cause to the over consumption of water and the excessive use of spirituous liquors among other things. Modern opinion tends to center about two foci. Hawkins (3) would have us believe that atrophic cirrhosis of the liver has no direct etiological relationship to syphilis.

He admits that there may be an indirect, or parasymphilitic relationship, but favors chronic alcoholism as the causative agent. Symmers (4) is equally emphatic in his belief that alcohol plays but a minor role in the etiology of atrophic cirrhosis, and that there is at least a certain group of cases of atrophic cirrhosis of the liver in which syphilis is a primary factor. To further minimize the importance of alcohol Symmers states that atrophic cirrhosis of the liver is equally common in Brahmins and Mohammedans, among whom the use of alcohol is religiously forbidden, and further, that the long continued administration of alcohol to experimental animals has at no time resulted in the production of atrophic cirrhosis. In a few cases (5) a condition similar to atrophic cirrhosis has been produced in experimental animals by the continued use of sclerotic poisons, such as chloroform, in conjunction with certain microorganisms and their toxins. One would expect, if Hawkins is correct, that in known chronic alcoholics the incidence of atrophic cirrhosis would be relatively high as compared with all cases of atrophic cirrhosis. This fact is

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largely mitigated by the findings of Symmers (4) and Formad (6). The former found but 3% of cases of atrophic cirrhosis among all autopsies performed on known chronic alcoholics, and the latter found but 6 cases of atrophic cirrhosis among 250 alcoholic patients that came to autopsy.

In studying our cases no attempt has been made to observe the incidence of chronic alcoholism for the reasons that this service includes people from all walks of life, and that many of the histories are too meager in this regard.

With the above exceptions the 2285 autopsies contain 58 cases of atrophic cirrhosis, 16 cases of early cirrhosis which generally have the characteristics suggestive of early atrophic or early syphilitic cirrhosis, 19 cases of syphilitic cirrhosis and 8 cases of Glissonian cirrhosis.

Type	No. of Cases	Percentage
Atrophic	58	0253
Syphilitic	19	0083
Early	16	0070
Glissonian	8	0035

#### ATROPHIC CIRRHOSIS

In our series of 2285 autopsies atrophic cirrhosis was diagnosed 58 times or 2.5%. This is somewhat higher than the results found by Symmers at Bellevue Hospital, 1.7%. His percentage is based on 4880 autopsies. The 58 cases may be tabulated as follows:

Total No. Cases of Atrophic Cirrhosis	58
No. of Cases of Atrophic Cirrhosis Associated with Histological Lesions of Syphilis	34
Average Age—53 yrs	

Males	29
Average Age—53.8 yrs	
Females	5
Average Age—48.4 yrs	
No. of Cases of Atrophic Cirrhosis not Associated with Lesions of Syphilis	24
Average Age—44.6 yrs	
Males	15
Average Age—43.2 yrs	
Females	9
Average Age—46.6 yrs	

Symmers observed the histological lesions of syphilis in 24 of 84 cases of atrophic cirrhosis, 28.3%. We find this association to be much higher, 34 in 58 cases, 60.3%. The age incidence is seen to run somewhat higher where syphilitic lesions are also present.

In the 34 cases of atrophic cirrhosis associated with syphilis in our series the distribution of cellular evidence of syphilis is as follows:

Lesion	No. of Cases	Percentage
Syphilitic Aortitis*	30*	88.2%
" Orchitis	16	47.0%
" Myocarditis	16	47.0%
" Pancreatitis	12	35.2%
" Adrenitis	12	35.2%
" Hepatitis	9	26.7%
" Leptomeningitis	5	14.7%

\*Lesions occurring less than five times are not recorded.

#### SYPHILITIC CIRRHOSIS

The average age incidence for the 19 cases in this group was found to be 41.1 years. The 12 males averaged 33.8 years, which is considerably below the average of 43.9 years for the 7 females. As in atrophic cirrhosis associated with syphilis the incidence of other lesions of syphilis is marked but considerably lower.

Lesion	No of Cases	Percent age
Syphilitic Aortitis	8	12.1%
" Myocarditis	7	36.8%
" Adrenitis	7	36.8%
" Orchitis	6	31.5%
Hepat Lobatum	6	31.5%
Syphilitic Pancreatitis	5	26.3%

" Myocarditis	9	60.6%
" Pancreatitis	8	53.3%
" Adrenitis	6	40.0%
" Orchitis	6	40.0%
" Leptomenigitis	5	33.3%

## GLISSONIAN CIRRHOSIS

## EARLY CIRRHOSIS

As previously stated cases placed in this group, while they favored either the atrophic or syphilitic groups, were too insufficiently developed for positive classification. There were 16 cases. Only one, a male aged 76 years showed no histological evidence of syphilis. The average age of the 15 syphilitics was 50.6 years, that of the 7 females was slightly more than half (37.6 yrs) that of the 8 males 60.3 yrs. Lesions of syphilis were present as below

Lesion	No of Cases	Percentage
Syphilitic Aortitis	10	66.6%

Of the 8 clear cut cases of this type of cirrhosis half are found in syphilitics. The average age is 26.5 years. The 3 females average 39 years and the 5 males average 17.2 years. The syphilitic lesions were found in two babies and two middle-aged adults. Old syphilitic lesions occurred in one case, orchitis syphilitica fibrosa in another, and congenital syphilis in the two babies.

## DISCUSSION AND CONCLUSIONS

If we combine the results of atrophic cirrhosis and early cirrhosis we find

Total No of Cases	Associated with Syphilis		Not Associated with Syphilis	
	Cases	Percentage	Cases	Percentage
74	49	66.6%	25	33.7%

Going a step farther and combining all four types we see

Total No of Cases	Associated with Syphilis		Not Associated with Syphilis	
	Cases	Percentage	Cases	Percentage
101	72	71.2%	29	28.7%

It would seem from the material available in this service that atrophic cirrhosis of the liver is relatively common and that its relationship to syphilis is more pronounced than in other services.

If the syphilitic type of atrophic cirrhosis may be properly combined with the early cirrhotic type the incidence of concomitant lesions of syphilis increases and if all four types may be combined the incidence swells enormously.

The low frequency with which other observers associate atrophic cirrhosis and syphilis may be partly explained upon the relative infrequency with which they diagnose visceral syphilis.

The lack of sufficient data prevents one from being more dogmatic in this matter, but certainly the frequency with which one finds well marked lesions of syphilis so constantly present in such a large percentage of cases of atrophic cirrhosis is of significance.

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# Focal Calcification of Heart Muscle; Case Report

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CALCIUM may be deposited within the cardiac tissue or precipitated directly into the endocardium. Healthy tissue never shows calcium salts deposited. Deposition of the calcium salts in dead or deteriorated tissue, however, is not very uncommon. (1) At first the process consists of a deposition of fine calcium granules, usually phosphates, within the broken up heart muscle fibers. These calcium granules may then coalesce, forming plaques, the latter gradually involving all elements of the heart substance. Scholtz (2) points out that there is no specific cause for this condition but that calcification can occur in the course of any pathological condition, which gradually leads to degeneration of the cardiac muscle fibers of diffuse or localized type. It has not yet been discovered just what rôle pathological conditions of the kidneys play with respect to its causing interference with calcium excretion and thereby probably increase in the total amount of free calcium salts, aiding the production of pathological calcification such as occurs in the myocardium.

It is the opinion of investigators along this line that the ultimate cause of pathological calcium deposition seems to lie in factors controlling the

calcium tolerance of the cell and in the character of the physio-chemical processes within the individual cells.

Calcium precipitation is an extremely rare condition, and the only two cases which have been reported involved the endocardium only. In both cases the condition was observed in association with calcium metastasis. By metastatic calcification is meant the direct precipitation into apparently normal tissue of the overload of circulating calcium salts produced by extensive bone destruction within the body. The precipitated calcium salts in such cases are occasionally found in the auricles of the heart (also in kidneys, stomach, and lungs). Here too, the endocardium of either right or left auricle is involved. Calcium metastasis could be considered a clinical entity composed of a clinical picture of primary bone destruction, finally superimposed by a second clinical picture somewhat suggestive of acute rheumatism. The real underlying causes of calcium metastasis are still unknown. However, the theory which seems plausible is the main causative factors consist of over-saturation of the circulation with calcium salts associated later on with a breakdown of the mechanism normally provided for excretion of calcium salts.



followed eventually by precipitation of the calcium overload in the places mentioned above

Calcium deposition in the myocardium has been shown by Diemer, Oberndorfer, MacFarland, and Lucas to be the result of extension of the process from the overlying pericardium

A few remarks on pericarditis calcuosa, so-called, or concretio pericarditis, may, therefore, be made here. A review of the literature up to 1923 by Case (3) shows that in only 13 instances has this been recognized in life. Cutler and Sosman (4) have recognized similar calcification in three patients with chronic heart disease.

In one case, the endocardium, pericardium, and myocardium were all involved.

Wells (5) found 4 cases of similar type (pericarditis calcuosa) out of 128 cases of pericardial adhesions from a total 1,000 autopsies.

Calcium deposits in the bundle of His has been reported by Waldorp (6) (1924).

Calcification of the heart may be demonstrated intravital if extensive enough. In such instances one may even succeed in differentiating it from pericardial calcification. Small calcium foci, however, cannot be demonstrated by X-ray during life. Small fine solitary calcium foci within the heart wall may be sometimes overlooked at necropsy, as in case herein reported. This may be avoided to some extent by taking X-rays of the removed autopsy specimens whereby very fine calcified areas are localized. Such autopsy radiographic work if carried on systematically will show

that the myocardial calcification is not so very rare as is believed.

X-ray is a very important aid for pathologists in research for small calcium foci and for other changes which cause radio-graphically sufficient differences of tissue density.

Cardiac degeneration due to obliteration of the coronaries with associated calcium deposition have been reported by Buins, Askanazy, and Scholtz (7). Coats and Hedinger described cases (one each) in which myocarditis was due to sepsis. Weichert reported a similar case in which the myocardial damages in which the calcium deposits were found were due to sepsis. Tily described a case of bichloride poisoning resulting in myocardial changes associated with calcification of the heart muscle.

Two cases, one by Roth and another by Siebenmann, have been reported in which there was a combination of metastatic calcification and that due to or associated with myocarditis.

#### CASE REPORT

W. L., colored male, age 47 was admitted to the Memphis General Hospital October 27, 1926 at the request of the Social Service Bureau. As the patient was in the state of coma, it was impossible to get a reliable history. However there was no knowledge of any previous illness until three weeks before the entrance, when his feet and ankles began to swell.

Physical examination showed heart apex 3 cm outside ant ax line. Systolic murmur at the apex and short diastolic murmur down the left sternal border. At the bases of the lungs there were coarse and fine rales with unimpaired resonance.

There was marked edema of the subcutaneous tissue.

Blood pressure 100/150. Temperature 98.6, pulse 90.

Blood N P N 1625, Creatinine 568,  
Uric acid 8.42

Total leukocytes—9,450, P. N 88% L  
10%, L M 11%

Total erythrocytes—3,590,000 Hb—70%  
(sahli)

The Wassermann test was negative

The urine contained slight trace of albumin and a few red cells

The clinical diagnosis was Malignant Hypertension, Myocardial Insufficiency, Uremic Coma

#### Treatment

Blood was removed twice by reimpuncture. October 30, 200 cc were drawn, and 400 cc of Fischer's solution were given intravenously. On November 2, 300 cc of blood were drawn and 500 cc of Fischer's given. 1 ampule of digifolin was given every four hours October 28, 29, 30, then discontinued. Patient was given the Karrell diet beginning November 1st.

The temperature during the following week ranged from 95 to 99.6. The pulse ranged from 86-124. On November 2 the blood pressure dropped from 170/120 and practically all of the oedema had disappeared.

On November 3, the blood showed—N P N 24615, creatinine 7.27 CO<sub>2</sub> 42 vol per cent. Sugar 0.148 mg.

On November 6 the patient died without having regained consciousness.

#### NECROPSY

The body was that of a negro male well developed but somewhat emaciated, 174 cm in length. There was a conjunctivitis, a pyorrhea, alveolaris, and dental caries. There was also a denuded surface on anterior chest wall, scars and wrinkling over both tibiae. Axillary, inguinal and epitrochlear lymph glands were enlarged. A penile scar, and a large denuded surface over the sacrum, obviously a bed sore were present.

#### INTERNAL EXAMINATION

Peritoneal cavity—There were fibrous adhesions between the omentum and liver and omentum and spleen. There was a mucosal ulceration in ileum just above the cecum 2x3 cm brownish in color and edges smooth,

not quite perforating. The liver seemed smaller than normal, firmer and was adherent to anterior chest wall. The spleen was adherent to diaphragm and omentum and seemed smaller and firmer than normal.

Pleural cavities. There were dense fibrous adhesions on the right lung between parietal and visceral pleurae, also between the visceral pleura and pericardium and diaphragm. There were 560 cc straw-colored fluid in left pleural cavity. Both lungs were soft and juicy.

Pericardial cavity. There was a fibrinous exudate over the entire pericardial cavity. There were large waxy patches on left ventricle and left auricle. The heart was markedly enlarged, apex reaching to 6th interspace, anterior axillary line.

Heart—Weighed 580 grams. The aortic mitral and tricuspid valves were thickened. There were silvery streaks and yellowish areas in the reddish myocardium. The wall of left ventricle was 2½ cm thick.

Aorta. Presented thickened, wrinkled, bark-like appearance.

Lungs. They were soft and juicy on cut surface, serum exuded and cut surfaces presented dark, reddish appearance.

Liver. Weighs 1100 grams. There were dense adhesions. The liver was firmer than normal. There were numerous hard contracted areas throughout. There was a small calcified area on the anterior surface. On cutting the liver was resistant to the knife and presented a reddish color. The gall bladder and ducts were negative.

Spleen. Weighs 11 grams. It was firmer than normal with thickened capsule. It cut with increased resistance, and had a reddish color.

Gastro-intestinal tract. About 4 cm above the cecum there was an ulceration 2x3 cm, edges smooth, brownish, necrotic tissue in center. It involved all coats of intestines, but did not perforate.

Kidneys. Right weighed 65 grams. It was small, firm, contracted, and deeply scarred. The capsule was difficult to strip and left a finely granular surface. On cut surface, the cortex was slightly narrowed and the vessels stood up above the surface slightly thickened. The left kidney weighed

100 grams, vessels stood up above the surface, cortex not strikingly narrowed

Brain Some slight edema, otherwise negative

Microscopic Heart section revealed a slight hypertrophy of the myocardium, a rather marked increase of connective tissue. The walls of the blood vessels were thickened. No exudate was seen on the epicardium. There were irregular spotted areas of calcification (see Figure 1)

Pancreas Section revealed a marked increase of inter- and intralobular connective tissue. Blood vessels thickened

Kidneys Section revealed an enormous thickening of the walls of the largest blood vessels. The medium sized blood vessels showed hyperplastic intima. The arterioles were not very markedly thickened. The capillaries were congested and distended with red blood cells. There was marked increase of intertubular connective tissue

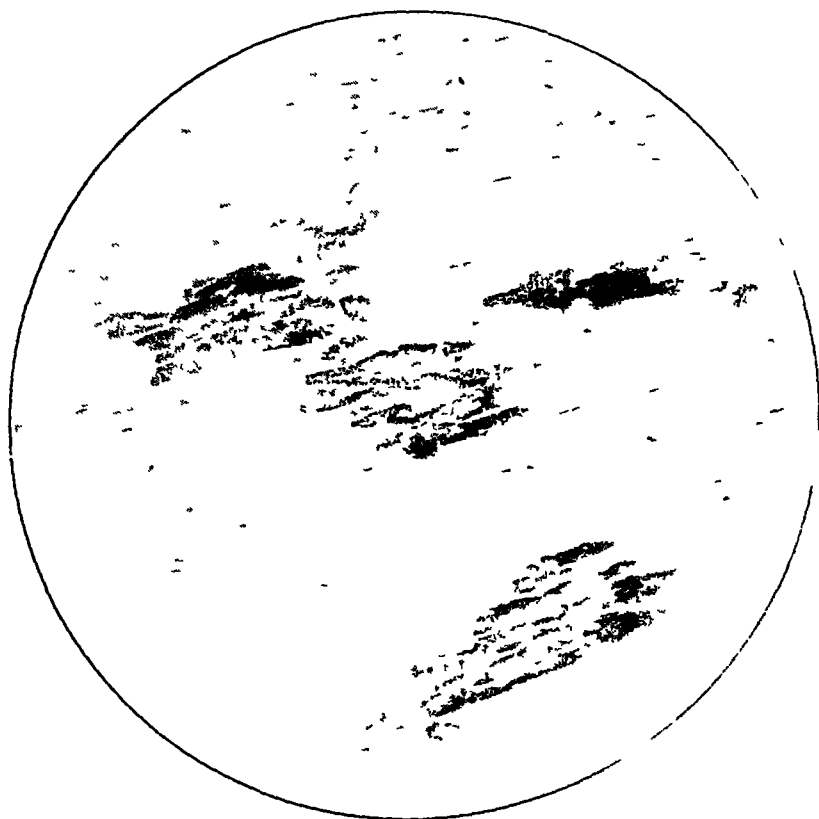


FIG 1 Microscopic section of cardiac muscle showing focal necrosis and calcification

Lungs Section revealed marked thickening of the walls of the larger blood vessels. There was chronic passive congestion and some emphysema

Liver Section revealed a marked chronic perihepatitis and marked chronic passive congestion

Spleen Section revealed marked chronic congestion, a marked thickening of the walls of the larger blood vessels

and large and small aggregations of small round cells throughout the section. The tubules were atrophied and there were numerous hyaline casts. Some of the glomeruli appeared normal and others showed increase of the endothelial elements of the glomerular tufts. Others showed hyaline casts of the glomerular tufts while still others were atrophied and showed marked fibrosis with

fibrous tissue growing in from the capsule to the glomerular tuft

#### Anatomical Diagnosis

Primary Malignant hypertension (gen-  
uine contracted kidney sclerosis and ne-  
phritis) chronic myocarditis with spotted  
calcification, syphilitic mesaortitis, chronic

passive congestion of thoracic and abdom-  
inal viscera, acute fibrinous pericarditis,  
syphilitic ulcer of the ileum

Subsidiary conjunctivitis, dental caries,  
pyorrhea aleolaris, penile scar

Cause of death Malignant hypertension  
with resulting uremia

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# Status Lymphaticus

By DR. HENRY M. RAY, M.D., *Pittsburgh, Pennsylvania*

**T**HERE is no generally accepted definition of "Status Lymphaticus". This condition clinically is at least in part related to certain constitutional defects variously designated under the terms laryngismus asthma thymicum, constitutio lymphaticus status thymicolymphaticus and others. All of these conditions described at different times by different observers, represent in all likelihood different manifestations and degrees of the same constitutional defect which was first mentioned more than 300 years ago by Felix Plater, who in 1614, reported the sudden death with no apparent cause of a five month's old boy whose most prominent pathologic finding at autopsy was the enlarged thymus. Thus the thymus was made to bear the etiologic burden on the basis of compression of the trachea and adjoining vascular structures and autonomic nerve trunks until the masterful publication in 1858 by Friedleben who established the dictum "Es gibt kein asthma thymicum" and denied that the symptoms were due to pressure. This view was later supported by Paltauf who based his conclusions on a vast amount of pathological material.

Status lymphaticus may be defined as a constitutional defect usually hereditary but occasionally acquired,

characterized clinically by definitely peculiar changes in the external configuration, lowered immunity to infection, increased susceptibility to chemical and physical agents and frequently sudden death, physiologically there is an impaired function of the autonomic nervous system, the gonads and adrenals and pathologically, hypoplasia of the cardio-vascular system, arrested development of the chromaffin system, adrenals and pathologically hypoplasia of the lymphoid tissue throughout the body including the lymph follicles of the spleen and hyperplasia or arrested involution of the thymus gland.

Experimental work on status lymphaticus establishes the close interrelation between the thymus and adrenals. In rabbits and rats, suprarenalectomy is followed by rapid regeneration and hyperplasia of the thymus and lymphoblastic tissue. It was first demonstrated by Lewis that removal of the suprarenals in rats reduced their resistance at least 400 times. In fact, it was later shown by Scott, Take and Marine and Jaffe that suprarenalectomy in animals produces greater lowering of resistance and hypersusceptibility than any other known experimental procedure. It is interesting to note that the immunologic response is not impaired in as much as the suprarenalectomized

animals retain their capacity to produce antibodies in spite of their lowered resistance. Thus as observed by Tanabe, cases of status lymphaticus in the Japanese army, while manifesting violent reactions to usual doses of typhoid vaccine showed no impairment in their titre of agglutinin production.

The fact that too much emphasis has in the past been placed on the thymus in the etiological role is responsible for the diversity of opinion in the interpretation of status lymphaticus and indeed as recently as 1927 it was asserted by Greenwood and Wood that the term status lymphaticus is a medical myth. Such an unfortunate assertion appears all the more inconsistent to one who has spent any time in the dead house and observed the constant pathologic anatomy of this condition. Status lymphaticus is certainly a distinct pathological entity and to a certain extent also a distinct clinical entity. The thymus plays only a secondary part in the picture and its size depends on the stage or degree of the lymphoplastic reaction at the time.

A clearer conception of the role of the thymus in this condition is hardly possible until more is known of the physiology of the gland. I have reason to believe that the thymic cells are really lymphocytes and that the gland is essentially a lymphoblastic structure. The thymus increases rapidly in weight to the beginning of the third year, remaining stationary until the seventh year when it increases slightly and declines about the eleventh year. At the age of puberty the gland begins to undergo a progressive involution or

atrophy. I am not in accord with the prevalent view that the thymus disappears completely after middle age. In 800 autopsies on individuals past 45 I have observed evidence of glandular remains by histological examination of the anterior mediastinal pad of fat in 20 per cent of subjects, in the majority of whom there was no naked eye evidence of thymic remnants.

That the thymus gland begins its permanent involution with sexual maturity is evidence of the close interrelation with the sex glands as well as the other endocrine structures, notably the thyroid and adrenal. It is interesting to note that during the involutionary stage there is regeneration of reticular cells, thymic cells and Hassall's corpuscles, but regeneration cannot keep pace with the involution process except in pathological involution due to infections, intoxications and X-ray exposure, where regeneration may be rapid and complete.

That the thymus has an internal secretion has not been proved. Rather are most inclined to regard it as a lymphoid structure. It has been experimentally established that thymectomy is not followed by important symptoms and that the organ is in all likelihood not essential to life. Its most important contribution is in the nutrition and growth up to the time of sexual maturity, particularly in the development of the bony system. Thus the outstanding effects of experimental thymectomy are referable to the calcium metabolism and deficient ossification. Some attribute to the gland an ability to form antibodies and a detoxicating function (Barbara).

In the relation to the hemopoietic system the thymus like the other lymphoid structures is an important source of lymphocytes and possibly also of eosinophils. In all likelihood it has no bearing on red cell formation.

Interrelation of the thymus with the glands of internal secretion is seen in the effects of castration, suprarenallectomy and thyroparathyroidectomy. While removal of the sex glands does not stimulate the thymus to growth it certainly inhibits its involution. Removal of the suprarenals not only prevents involution but also stimulates regeneration. The thyroid gland on the other hand appears experimentally to have an opposite effect since thyroidectomy reduces the growth of the thymus and hastens involution.

Pathologically, the picture of active status lymphaticus is a very definite one. The thymus is enlarged and the microscopic picture depends upon the age of the individual. The medulla shows invariably, lymphoid hyperplasia while the cortex may be sclerotic. An eighteen months' old male child upon whom I performed a necropsy following sudden death from violent dyspnea and cyanosis, presented a relatively huge thymus which weighed 86.5 grams. Symmers states that in the large series of necropsies at Bellevue Hospital the thymus in typical status lymphaticus averaged 25 grams. The spleen is usually enlarged, sometimes palpably so; the Malpighian follicles are increased in number and size and endothelial elements are occasionally hyperplastic. While there is no demonstrable enlargement of the superficial regional lymph nodes, the lingual and faucial

tonsils and naso-pharyngeal lymphoid tissue are markedly hyperplastic and there is definite hyperplasia of the intra-thoracic and abdominal nodes, Peyer's patches and solitary lymph nodes of the intestine. Collections of lymphoid cells are found in the viscera, particularly the liver. The thyroid is likely to be enlarged and the suprarenal bodies, particularly the medullary substance and extra-glandular chromaffin tissue show hypoplasia. The cardio-vascular system is underdeveloped, the vessels narrow and the walls thin and delicate, lacking elastic tissue and deficient in muscle tissue. Myocardial degeneration, hemorrhages and atheromatosis are prone to supervene. The osseous system shows evidence of impaired calcification and in younger subjects rickets is often associated.

In the recessive types the thymus has been practically entirely replaced by fat and the hyperplastic lymphoid structures show atrophy with sclerotic changes depending upon the stage of involution. The skeletal changes and body configuration of course remain unmodified.

Clinically the children are well nourished, gracefully formed, the skin is marble-like and velvety and the hair is fine and silky. In adults too the skin is pale and delicate, the facial and axillary hairs are scanty, there is very little or no hair on the chest and in the male the abdominal hair is absent and the distribution of the pubic hair resembles that in the female. The thighs are gracefully arched, the waist narrow and external genitalia small. In the female the usual graceful lines are exaggerated and the

axillae contain fat pads with little or no hair. Most of the cases I have seen in females have been blondes.

There is usually a lymphocytosis, hypotension and hypoglycemia. The coagulation time is prolonged. I have never failed to find the lingual tonsils hypertrophied and this is particularly valuable, as it offers an important sign when one is examining a subject who has had a tonsillectomy.

Children mature slowly and secondary sex characteristics are delayed, the musculature is flabby and there is lack of resistance to fatigue and infection. While sudden death sometimes occurs and dramatically so, most cases are probably well able to withstand traumatism and to overcome infection.

The pathogenesis of status lymphaticus is not clear. The condition is obviously congenital although there is no evidence that it is hereditary. Infections in early life probably play an important part.

The actual cause of death in this condition is by no means clear. Many deny that mechanical pressure of an enlarged thymus can itself be responsible. Schule has shown that it requires a weight of 1000 grams to actually close an infant's trachea. In the baby with the huge thymus whose necropsy I have referred to, the gland covered the entire right heart and was adherent to the pericardium. The anatomic signs were those of asphyxia. It is difficult to ignore not alone the possibility of compression of the vessels and right heart but also the influence, particularly in a stage of acute swelling, on encroachment of the thoracic inlet and the effect of pres-

sure on the vagi and recurrent laryngeal nerves with subsequent spasm of the glottis.

In adults the cause of death must be sought for elsewhere. None of the many expounded theories is in itself acceptable. To state that the condition is a hypersusceptibility to physical and chemical agents is no etiologic elucidation. Some state that it is a constitutional defect with increased vagus tone, insufficient chromaffin tissue and inherent weakness of the sympathetic system. Others, notably Symmers, believe that anaphylaxis plays an important part and that sensitization and shock result from the liberation of certain nucleoproteids from the massive and widespread necrosis of the centers of the germinal follicles. It is likely that all of these factors combine to contribute to the final outcome. In the sudden so-called thymic deaths of infants, one is reminded of the pathology in the experimental anaphylactic deaths of animals. I have observed the marked fluidity of the blood, the dilated right heart, the cerebral edema with scattered minute brain hemorrhages, the congestion of the viscera especially the lungs and the petechial hemorrhages of the visceral pleura, epicardium and peritoneum. In adult subjects, the majority of deaths are due to the failure of the inherently weak cardiovascular system. Thus in a number of necropsies on steel mill workers, six of which manifested anatomic signs of status lymphaticus, five showed degenerative myocardial changes with cardiac dilatation and one a thirty-two year old Lithuanian, died suddenly with rupture of a small aneurysm.



of the anterior communicating artery of the circle of Willis. The hypoadrenal state is known experimentally to increase the susceptibility to shock and infection and in its relation to the effect on disturbing the harmonious balance of the endocrine system with the frequently resulting hypoglycemia which occurs in the human subject of this disease, one must consider an existing autonomic imbalance with inevitable disturbance of the metabolism.

*Medicolegal Considerations*—Great importance attaches to status lymphaticus in legal medicine, particularly in the matter of sudden death. This was first recognized by the Vienna school of pathologists, notably by Paltauf and Kolisko. Among 5652 autopsies in Bellevue Hospital, Symmers recognized 457 cases of which most were active, some recessive and others partial. It must be remembered that in later years the thymus and lymphoid tissues atrophy. In a review of 2012 necropsies of my own I find recorded in the anatomic diagnosis status lymphaticus either active or recessive, 180 times. It is to be noted that status lymphaticus will be more often recorded in a series of necropsies in a medical examiner's or coroner's service than in a routine hospital postmortem service, in virtue of the fact that the former is more likely to deal with cases of sudden death and suicides. Many of the subjects of status are mentally deficient and manifest evidence of nervous and mental disease. Thus Bartels observed in an analysis of 122 cases of suicide that anatomic evidence of status was constantly present. Ohlmacher found definite

signs of status in the great majority of fatal cases of epilepsy.

In infancy, many cases of sudden and unexpected death terminating with rapidly increasing dyspnea or cardiac failure, reveal at autopsy that the thymus is much enlarged and the evidence is not altogether conclusive that death can be attributed solely to mechanical pressure on the trachea or great vessels. In adult life, death is more frequently referable to the complications following the hypoplasia of the cardiovascular system. The small heart and narrow aorta with the delicately thin vessel walls are subject to functional disorders, inflammatory lesions, aneurysmal dilation and rupture. Thus we have the sudden and unusual deaths in bathers, or after insignificant trauma or following the careless administration of foreign protein or other substances intravenously. Necropsy records show that a large proportion of rapidly fatal cases of infectious diseases are subjects of status lymphaticus. Subjects with generalized Hodgkins disease usually show anatomic signs of status and many of the endocrinopathies are associated with status in various ways. Hypoplasia of the genitals is common and the bodily configuration has many of the features of pituitary adiposogenital dystrophy.

The case of the young chorus girl twenty-one years old is an example of the marked hypoplastic state of the vessels in this condition and emphasizes the importance of status lymphaticus in legal medicine. It appears that this girl while walking with an escort engaged in an argument whereupon he pushed her vehemently

and she fell to the side-walk, becoming unconscious and dying before the arrival of medical aid. The necropsy of this beautiful blonde, showed the smooth pale marble-like skin, silky hair, total absence of body hair except a scanty amount over the pubes and very little over the two distinct fatty axillary pads. The breasts were small, the waist extremely narrow and the pelvis extremely wide with flaring ilia and gracefully arched thighs. The lymphoid tissue was everywhere hyperplastic, the thymus weighed 24.5 grams, the spleen was enlarged and presented huge Malpighian follicles which showed histologically, necrotic centers. Peyer's patches were large thickened swollen masses of lymphoid tissue and the solitary follicles were prominent. The adrenals were small and showed intramedullary hemorrhagic infiltration. The heart was unusually small, the myocardium flabby and the aorta was thin, inelastic and actually no larger in caliber than the small finger. The vessels at the base of the brain were collapsed, narrow, actually the thickness of tissue paper and upon immersion in water it was interesting to see multiple small thin walled aneurysmal sacs, one of which had ruptured with fatal hemorrhage.

#### *Summary and Clinical Significance*

—It has been the purpose of this paper to bring out the practical clinical aspects of status lymphaticus. Only too often one hears expressions from apparently scientific clinicians, to the effect that status lymphaticus does not exist in fact and that the term is used by many, mostly pathologists and occasionally clinicians, to mask their ignorance in certain clinical states and

more particularly in ascribing to it the cause of death where the actual cause is otherwise obscure. It has been my experience that such expressions emanate from men who rarely, if ever, visit the postmortem room. Such unfounded opinions are easily impressed upon the minds of the younger clinical associates. While most of our younger men are well trained in the practical aspects of clinical laboratory procedure, it is extremely difficult to detect any active interest in postmortem activities. The average interne breathes a sigh of relief after he has completed his attendance at the compulsory number of necropsies. Many a postmortem is performed with only the pathologist and the pathological intern present and this in spite of the fact that the necropsy is announced and advertised on the bulletin board several hours before the postmortem is undertaken. It should be the duty of the chiefs of service to set an example by attending all postmortems and thereby stimulating the proper scientific attitude and habits of the younger men.

There is another group of clinicians who while recognizing the pathological status of this condition, express the opinion that status lymphaticus is entirely a pathological entity and can never be recognized during life. When one observes these cases on the postmortem table again and again, the constant pathologic findings are so pathognomonic as to make an indelible impression. With a visual picture of the anatomic defects and pathological changes in these subjects and keeping in mind those outwardly discernible characteristics already

enumerated, the changes in skin texture, the configuration, the lymphoid hyperplasia (as for example the tonsils and more particularly the lingual tonsils) that can be detected by thorough inspection, the hypotension, the often associated though slight mental peculiarities, the relative lymphocytosis, the hypocalcemia, the hypoglycemia, a possible history of rickets in early life, the susceptibility to repeated infection, etc., the clinical recognition is no longer a difficult task.

Most of the cases do not die from trivial traumatism or minor operations and in fact this is a rare occurrence. By far, most of them attain maturity and as time goes on, present certain symptoms which can in part at least be explained by the inherent constitutional hypoplastic state. When the clinician has all these facts in mind he does not fail to look for

these anatomic signs, he studies the cardio-vascular response, he studies the blood count and blood chemical values with particular reference to sugar and calcium, he orders a metabolism determination and makes other clinical tests to detect any pathological change in the endocrine physiology, as for example, the adrenal response with the Goetsch test. Knowing the tendency toward cardio-vascular hypoplasia, he can caution the subject against undue physical or emotional stress productive of sudden blood pressure changes which are unsafe for a delicate thin walled vascular system. The data enables him to advise X-ray therapy, calcium administration, dietary considerations, and certain endocrine products to fit the individual case, as for example, parathyroid, thyroid, pituitary, adrenal substance or sex glands either singly or in combination,

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# Two Cases of Cardiovascular Anomaly\*

## I. Vegetative Pulmonary Endarteritis Complicating Persistent Ductus, II Hypoplasia of Aorta.

By NEWELL W. PHILPOTT, M.D., C.M., *Chicago, Illinois*

**S**TUDY of congenital cardiac disease offers much of interest and constantly affords many fascinating problems. It is a well established fact that congenital cardiac defects act as a predisposing factor in the occurrence of infectious heart disease. Cardiac anomalies, especially those of the non-cyanotic group, such as defects in the interventricular septum, bicuspid semilunar valves, and patent ductus arteriosus are commonly the site of infective processes. In a series of 656 cardiac anomalies collected by Abbott the total incidence of inflammatory heart disease was 129 cases, or 19.6 per cent, of which 96 cases were in the non-cyanotic group and 39 in the cyanotic group. The first case which is now being discussed is classified in the non-cyanotic group and is complicated by inflammatory heart disease.

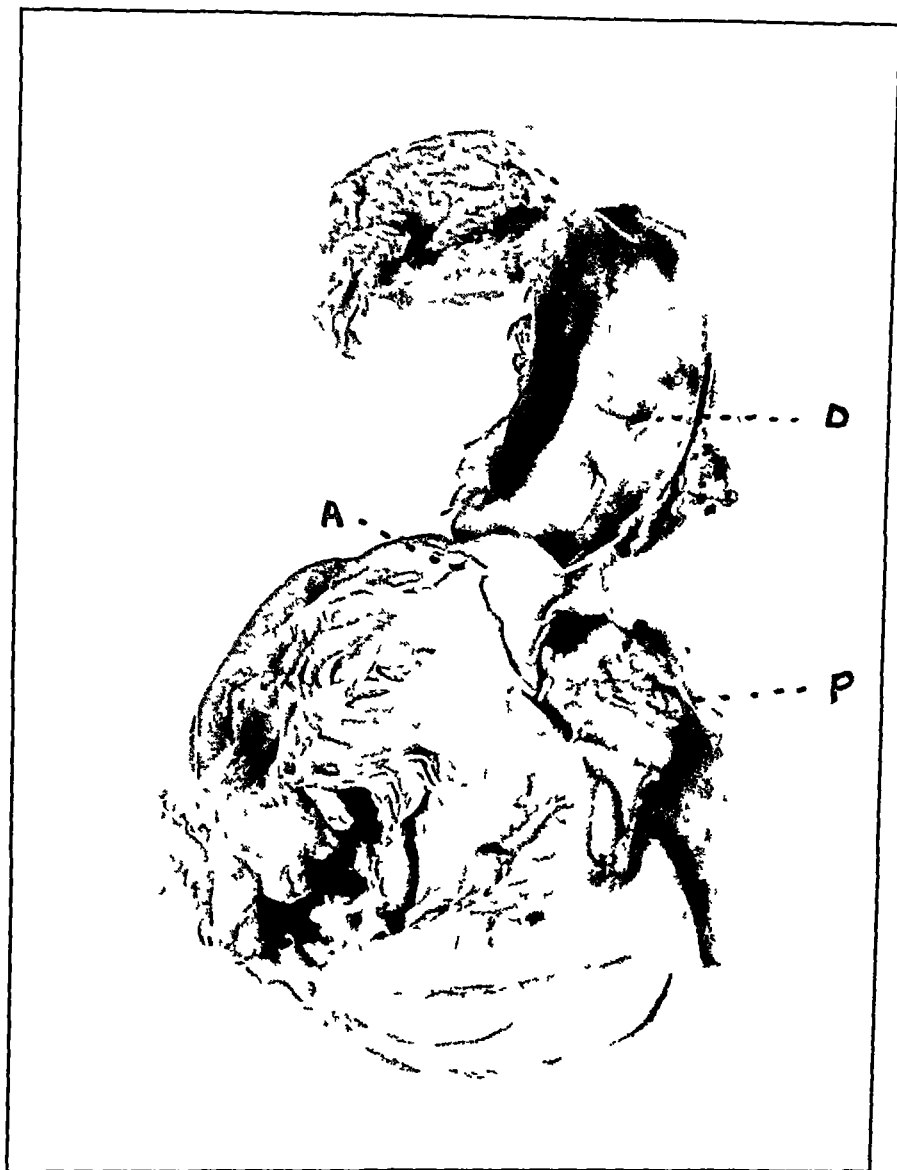
The literature records twenty-three cases of patent ductus arteriosus complicated by an infective endarteritis, situated at the pulmonary opening of the ductus and in the adjacent portions of the pulmonary artery. Of these, twenty show an accompanying valvular endocarditis affecting one or more of the heart valves. In only three (Krzyszkowski, 1902, Hamilton and Abbott, 1914, Schlaepfer, 1926) were the heart valves intact with the inflammatory process restricted to the pulmonary artery and the ductus arteriosus. This present case makes the fourth on record of this rare condition.

### REPORT OF CASE

#### CASE No. I

Our first case illustrates clearly the condition of vegetative pulmonary endarteritis in association with a persistent ductus. Botalli and superimposed upon an already damaged vessel

\*From the Pathological Laboratory of the University of Michigan, Ann Arbor.



No 1 Heart opened to expose the aorta and pulmonary artery A Aortic cusps D Opening of widely patent ductus of Botalli at aortic end P First part of pulmonary artery showing very marked vegetations in the lumen above the cusps Note The aortic cusps aorta and opening of the ductus at the aortic end are absolutely free from any infective process

November the family doctor informed the parents that the child had a heart condition. For two months previous to admission the child had a hacking cough and lost  $7\frac{1}{2}$  lbs in weight. Abdominal distention also gradually developed.

*Personal History* Child was a full term baby. Delivery was normal, the color and respirations did not appear out of the ordinary. Two years ago, 1925, had measles and chicken pox. The family doctor states that for the past two years the child has had frequent, severe attacks of tonsillitis.

*Family History* Father and mother are both well. The other two children are in excellent health. The mother's blood Wasserman is negative on two occasions. The other members have not been tested. None in the family have been treated for blood disease.

*Physical Examination* The patient is an acutely sick child who gives the appearance of having been ill for some time, and of having lost considerable weight.

*Positive Findings* There are many râles at both lung bases. Pulse rate is 160 per minute. There is a marked enlargement of the heart to the left and a slight enlargement to the right. The left border is in the anterior axillary line. There is a diffuse pulsation over the apical and pulmonary areas. The sounds are rapid and regular throughout. A very loud murmur, systolic in time, is heard best in the second interspace to the left of the sternum. This is transmitted laterally to the axilla and up the vessels on the left side. The abdomen is distended and tympanic. The spleen is markedly enlarged with the lower border two finger breadths below the umbilicus. Liver edge descends four cms below the costal margin. Some tenderness is noted over the abdomen, but the child appears generally hypersensitive.

*Laboratory Findings* The urine shows albumin four plus, many casts, a large number of WBC, which are mostly lymphocytes, and an occasional RBC. The blood hemoglobin is 34%. RBC are 3,400,000, WBC are 17,000 of which 72% are polymorphs.  $\text{CO}_2$  combining power is 28.7%. Blood W. cream is 3 plus repeat 2 plus, and 4

plus on a third test. Blood culture report is hemolytic streptococci. X-ray reports an area in the second interspace on the left of increased density suggestive of tuberculosis.

*Course* Was rapidly downhill. During her stay in hospital she ran an irregular temperature which gradually became higher and before death reached a peak of 106 degrees. Her pulse raised in direct proportion to her temperature, ranging from 120 to 180 per minute. The respirations gradually became more rapid and death occurred six days after admission on 1/30/28.

*Final Clinical Diagnosis* Septicemia. Congenital syphilis. Endocarditis and pericarditis. Congenital heart (patent ductus arteriosus?). Subacute glomerular nephritis. Secondary anemia. Abscesses in spleen and liver.

The autopsy was performed five hours after death at 9 30 A.M. 1/30/28.

PROTOCOL (ABRIDGED)

adhesions which tear easily Liver is 8 cms below the ensiform and  $5\frac{1}{2}$  cms below the costal border in the right mid-clavicular line Spleen extends obliquely below the left costal border for a distance of 7 cms

*Thoracic Cavity* Left pleural cavity contains 100 cc of thick, yellow, purulent fluid There are many adhesions from the posterior surface to the thoracic wall The right pleural cavity contains 30 cc of a turbid fluid which is slightly blood tinged No adhesions are present on this side Heart lies transversely in the thoracic cavity, and is definitely enlarged The apex is behind the 5th rib in the anterior axillary line The right border is 2 cms to the right of the mid-sternal line Left lung is collapsed with the lung borders 7 cm apart in the anterior mediastinum A small amount of thymic tissue is present in the anterior mediastinum

*Pericardium* There is a slight increase in thickness toward the base The tension is definitely increased The sac contains 50 cc of a clear yellow fluid

*Heart* Measures  $9 \times 7 \times 3\frac{1}{2}$ , weighs 180 gms Is much larger than the cadaver's right fist All the cavities contain a large amount of cruor The apex is formed chiefly by the left ventricle which is in firm rigor There is an occasional subserous petechial hemorrhage toward the base On opening the aorta it is noted that the ductus arteriosus is patent with an opening in the arch measuring 4 mm in diameter It will admit a large probe with ease and the total length is 75 cm

*Right Heart* Left ventricular wall measures 15 mm, and appears markedly hypertrophied Musculature is light brown with small whitish areas about 2 mm in diameter noted throughout The endocardium is smooth and shining with exception of the portion in the left auricular appendage corresponding to the attachment of a parietal thrombus The mitral valve admits the index finger The cusps are not roughened and appear normal The aortic valve admits the thumb No evidence of vegetations or roughening of the cusps is present

*Right Heart* The right ventricular wall measures 7 mm and also appears hypertro-

phied The musculature resembles that found on the left side The endocardium is smooth and shining throughout The tricuspid valve admits 2 fingers with difficulty The cusps show no gross pathological lesion The pulmonary valve admits the thumb with difficulty, the cusps appear normal The foramen ovale is closed

*Coronary Vessels* Are patent and appear normal throughout

*Left Lung* Measures  $12 \times 10 \times 3\frac{1}{2}$  cm, and weight 190 gms The surface is roughened corresponding to the attachment of the adhesions, and there is a marked thickening of the pleura The lung is atelectatic throughout Cut section shows many firm, dark areas raised above the surface which appear to be patches of pneumonia There is a definite increase of fibrous tissue surrounding the smaller bronchi and bronchioles The smaller branches of the pulmonary artery, more marked in the lower lobe, show many thrombi of different ages, some are organized while others are of a more recent nature In some portions the vessel wall shows an aneurysmic dilatation Many corresponding infarcted areas are present, some of which appear secondarily infected No tubercles are found

*Right Lung* Measures  $14 \times 13 \times 4$  cm, weighs 200 gms The surface is smooth Many pneumonic and infarcted areas are also noted on this side especially in the lower lobe There are also many fibrous bands radiating from the smaller bronchi and bronchioles

*Pulmonary Vessels* The opening of the ductus arteriosus is 2 cms from the superior border of the pulmonary cusps On the inferior and lateral wall  $1\frac{1}{2}$  cm, from the pulmonary cusps an area, 3-2 cm, is covered by cauliflower vegetations These are adherent to the vessel wall and project into the lumen causing a partial obstruction The opening of the ductus is situated on the opposite side on the superior and lateral aspect

*Thoracic Aorta* Is normal in size The intima appears normal throughout From the opening of the ductus in the arch there is a freshly formed blood clot extending into the lumen of the aorta



No 2 Left lung with pulmonary artery exposed Note the large, round thrombus in the lumen with a definite saccular aneurysmic dilatation of the vessel at the corresponding point of attachment



No 3 Small branch of pulmonary artery in right lung completely obliterated by an infected thrombus



*Left Kidney* Measures  $10 \times 5 \times 3\frac{1}{2}$  cm, weighs 130 gms. The fibrous capsule strips with ease displaying a markedly congested surface which is smooth. Cut section gives a distinctly boiled appearance with the cortex raised above the surface of the medulla. The pelvis is not distended and there is no gross evidence of a pyelitis. No infarcts are noted.

*Right Kidney* Measures  $11 \times 4 \times 3$  cm, weighs 140 gms. Resembles the left in its gross appearance.

*Female Genitalia* Shows a normal development.

#### MICROSCOPIC FINDINGS

*Cord* Shows early syphilitic meningitis.

*Heart* Subepicardial fat shows serous atrophy. Heart muscle is well developed for age, but there is a degenerative fatty infiltration. Endocardium is thickened but there is a degenerative fatty infiltration. Endocardium is thickened, but there is no fresh process. Valvular endocardium is thickened but there are no vegetations.

*Aorta* Over the base there is a proliferative pericarditis. Higher in the aorta, at the isthmus, there are definite evidences of syphilis, the lesions being of some standing,—perivascular infiltrations and fibrosis with sclerosis of the media and intima and an older thrombosis on the wall.

*Pulmonary Artery* The wall of the ductus arteriosus and of the pulmonary artery shows definite old syphilitic lesions with a superimposed acute streptococcus viridans vegetative endarteritis, with ulceration of the wall and the formation of a mycotic aneurysm, filled with an infected thrombus—thrombo-endarteritis purulenta.

*Lungs* Show chronic purulent pleuritis with fibrosis of the pleura. There is a chronic pleuro-pneumonia with marked fibrosis of the interlobular septa. Atelectasis is alternated with dilated air-sacs. Large areas of fibrosis are present. There is a chronic purulent bronchitis. All the branches of the pulmonary arteries show an old obliterating endarteritis with thrombosis. On the older partial thrombosis there is a secondary vegetative process with a distinct tendency to suppuration, and to the develop-

ment of mycotic aneurysm. Through the lung are numerous hemorrhagic infarcts in various stages.

*Diaphragm* Shows on pleural side an empyema, on the peritoneal side a subacute peritonitis of less degree.

*Spleen* There is an extreme congestion with necrosis of the centers of many of the follicles.

*Gastro-intestinal Tract* There is a proliferative subacute peritonitis. Mucosa shows an atrophic catarrh.

*Pancreas* Shows atrophy but no signs of syphilis.

*Liver* Is a typical nutmeg liver with a localized chronic perihepatitis. There is no evidence of syphilis.

*Kidneys* Show a sub-acute glomerulotubular nephritis. Many glomeruli are in various stages of repair.

*Lymph-nodes* Show hyperplasia with proliferation of the reticulo-endothelium. There are no tubercles.

*Pathological Diagnosis* Mycotic aneurysm of the pulmonary artery opposite the mouth of the patent ductus Botalli (streptococcus viridans infection on an old syphilitic arteritis). Multiple organizing emboli in pulmonary arterial branches with hemorrhagic infarctions. Chronic pleuropneumonia. Atelectasis. Bronchopneumonia. Subacute empyema. Acute syphilitic meningitis of cord. Marked chronic passive congestion of liver and spleen. Sub-acute glomerulotubular nephritis. Diffuse proliferative peritonitis. Marked hyperplastic lymphadenitis.

#### DISCUSSION

*Clinical Findings* From the clinical aspect this case demonstrates very well the condition of persistent ductus Botalli being complicated by an infective process. Before the onset of the fatal illness the child displayed no

definite signs of a congenital heart lesion though she always appeared weak and pale. The last illness was preceded by frequent attacks of tonsillitis, a right-sided otitis media with a questionable involvement of the mastoid region. Other cases on record give histories of a very similar nature. Four have histories of a preceding rheumatic fever, repeated attacks of sore throat were a feature in the case reported by Sommer. Schlaepfer's report states that the onset of the fatal illness was preceded by a bilateral otitis media.

A review of the other cases on record show the physical findings to have a striking likeness. Diagnosis of the patent ductus is made by some or all of the following signs being present —

1—A thrill felt over the pulmonic area

2—Dullness in the upper spaces to the left of the sternum

3—Roentgen-ray reveals an area of increased density due to increased volume of the pulmonary artery. This is shown in the 2nd left interspace.

4—Accentuated pulmonary second sound

5—A murmur heard best in the pulmonic area and transmitted up and to the left

Our case shows —

1—A diffuse pulsation in the pulmonic and apical regions

2—Enlargement of the heart to the left

3—Pulmonic second sound markedly accentuated

4—Systolic murmur in the pulmonic area and transmitted up and to the left

The infective process is of a sub-acute nature, the course being progressively downwards. The average duration is from six months to one year. Two cases, Buchwald and Hamilton, lasted only two months while that reported by Boldero extended over a period of two years. The picture is that of a typical blood-stream infection; blood cultures have shown streptococcus viridans, staphylococcus albus, influenza bacillus, and pneumococcus. The present case proved by blood cultures taken before death and at autopsy to be a streptococcus viridans infection.

*Pathological Findings* The picture is typically that of a streptococcus viridans infection superimposed upon an active congenital syphilis. The lungs and pulmonary artery show old syphilitic lesions. Due to lowered resistance and mechanical strain, a vegetative endarteritis developed upon the intima of an already damaged pulmonary artery and ductus. The lungs contain multiple infarcts, abscesses, and areas of chronic pneumonia with an extensive empyema. A secondary peritonitis is present due to an inflammatory extension of the empyema through the diaphragm. The glomerulo-tubular nephritis is typical of that found in streptococcus viridans infections.

There is a definite localization of the vegetative endarteritis to an area in the pulmonary artery opposite the ductus opening and to the ductus wall. The three other cases on record show a very similar localization, those by Schlaepfer and Krzyszkowski have the process strictly confined to that portion of the pulmonary artery at

the ductus arteriosus opening Hamilton's case shows the pulmonary artery likewise involved but, in addition, the process extends along the wall of the ductus

Infarcts in the lungs, spleen, kidneys, intestines, skin and brain are found to be frequent complications Multiple abscesses in the lungs are common Thrombus formations in the smaller branches of the pulmonary artery with aneurysmic dilatations of the vessels, similar to those found in the present case, have been reported by Sachs, Kidd, and Krzyszkowski

This case also demonstrates the fact that the Wasserman reaction on the blood of women during the child-bearing period is often of no significance A mother who has borne one or more children and who is definitely syphilitic frequently has a negative blood Wasserman which will not become positive until she reaches the menopause In this present case the child gives definite evidence of congenital syphilis and had a positive blood Wasserman on four occasions The mother, on two examinations, is negative to the Wasserman test

#### SUMMARY

- 1—The child has congenital syphilis
- 2—Ductus of Botalli is persistent
- 3—At the age of six she develops a streptococcus viridans infection with a vegetative endarteritis of the pulmonary artery There is no accompanying endocarditis
- 4—The illness is of a sub-acute ending fatally after a period of six months
- 5—There are twenty-three cases on

record of patent ductus Botalli associated with a pulmonary endarteritis Only three in addition to the present report have an endarteritis of the pulmonary artery with no accompanying valvular lesion

#### Case No 2

##### Hypoplasia of the Aorta

Hypoplasia of the aorta commonly occurs in conjunction with a certain set of cardiac anomalies These include coarctation of the aorta anomalies of the aortic arch, bicuspid semilunar valves, persistent left superior vena cava and patent foramen ovale For this reason the condition of hypoplasia of the aorta is usually classified with congenital cardiac defects It occurs, however, as an isolated condition not in association with any cardiac anomaly and may be manifested by the aorta and its branches being markedly reduced in size often measuring only  $\frac{1}{2}$  the normal caliber

Much discussion has arisen as to whether this isolated condition is a true congenital cardiac anomaly or whether it is purely a post-natal lack of development Subjects of the thymico-lymphatic constitution possess an aorta which is hypoplastic Usually this hypoplasia is not pronounced, but occasionally we find the vessel markedly diminished in size, often suggesting a congenital defect On investigation these cases are found to possess other characteristics common to the thymico-lymphatic constitution such as a hyperplastic thymus generalized lymphoid hyperplasia and hypoplasia of the adrenal The condition of hypoplasia of the aorta

lunar valves, persistent left superior with no associated cardiac of circulatory defect is probably a manifestation of a definite constitutional type

### CLINICAL REPORT

Miss A. A., Aged 17

Was admitted to the University Hospital 2-13-28 with the chief complaints of dyspnoea, cyanosis, palpitation, and edema. She has always been delicate. At the age of 8 a swelling was first noted in her neck and at this time, she was not gaining in weight. At the age of 12 a specialist was consulted who prescribed "goitre pills." Shortly after, her symptoms became more marked and the pills were discontinued. When 13 years of age her family doctor found an enlarged heart and a "leaky valve." One year later, 14 years of age, she developed chills and fever. Endocarditis was suspected though the blood culture was negative. In November 1927, aged 16, edema was first noticed. This was accompanied by a slight cyanosis of the lips, fingers, and toes. She was digitalized for the first time in January 1928, one month before admission.

*Past History* Had influenza in 1918. No definite history of rheumatic fever, chorea, or scarlet fever. Had her tonsils removed at the age of four.

*Family History* Nothing to denote syphilis. No history of heart trouble on either side of the family.

*Menstrual History* Began at the age of 14 and were regular until four months ago. Since then have occurred more often and have been more profuse.

*Physical Examination* She is intensely dyspnoic, very cyanotic, propped up in bed, with a constant anxious expression. There is a marked pulsation of the neck vessels and the thyroid is enlarged.

*Lungs* Respirations 32 per minute. There is impaired resonance throughout with dullness at both bases. Many crackling râles are heard at both sides.

*Heart* Radial pulse is 104 per minute, weak, but regular. Cardiac dullness extends 12½ cms to the left and 3 cms to the

right of the mid-sternal line. Sounds are rapid, regular, and weak. A harsh systolic and diastolic murmur is heard at the mitral and aortic areas.

*Abdomen* The liver is enlarged and extends two fingerbreadths below the costal margin. There is a slight dullness in both flanks.

*Extremities* Show a massive edema most marked in the lower extremities.

*Laboratory Findings* Urine—albumin is slightly positive with an occasional hyaline and granular cast. Blood exam—95% hgb. R B C—7,000,000. W B C—12,300. Differential is not important. N P N of blood 682 mgms. Electrocardiogram shows a marked right ventricular preponderance.

*Course in Hospital* Death occurred two days after admission. Her temperature was always slightly sub-normal. Orthopnea and cyanosis became very marked. A venesection was done and 500 cc of blood withdrawn. This relieved her condition for only a few hours. The patient expired 2/15/28.

### Clinical Diagnosis

- 1 Aortic insufficiency and stenosis
- 2 Mitral insufficiency and stenosis
- 3 Congenital heart (type not specified)
- 4 Polycythemia (secondary)
- 5 Cardiac failure

The autopsy was performed two hours after death.

### PROTOCOL ABBREVIATED

Miss A. A., aged 17, 2-15-28

*External Examination* Body is that of a young adult female, 159 cms in length, of a light bony frame. There is a very marked generalized edema. Many small ulcers averaging 5 mm in diameter are present in the skin of the lower extremities. The face, mucous membranes, and extremities show a marked cyanosis, and there is a dark purple hypostasis present in the dependent portions. There is no clubbing of the fingers or toes.

*Abdominal Cavity* Contains 200 cc of a slightly turbid, yellow fluid.

*Pleural Cavities* Right pleural cavity contains 450 cc of a clear, yellow fluid.



No 4 Posterior view of thoracic organs, showing the marked hypoplasia of the aorta  
Case 2

The left pleural cavity contains 300 cc of a similar fluid

*Position of Thoracic Organs* On removing the sternum it is noted that the heart is very markedly enlarged with the pericardial sac lying transversely in the thorax. Both lungs are displaced laterally by the enlarged heart. Measurements of the pericardial sac intact are 18-13-8½ cm.

*Anterior Mediastinum* Is entirely filled by the enlarged heart and a hyperplastic thymus.

*Thymus* Extends downward over the anterior surface of the pericardium. The thymic tissue is markedly congested and definitely hyperplastic.

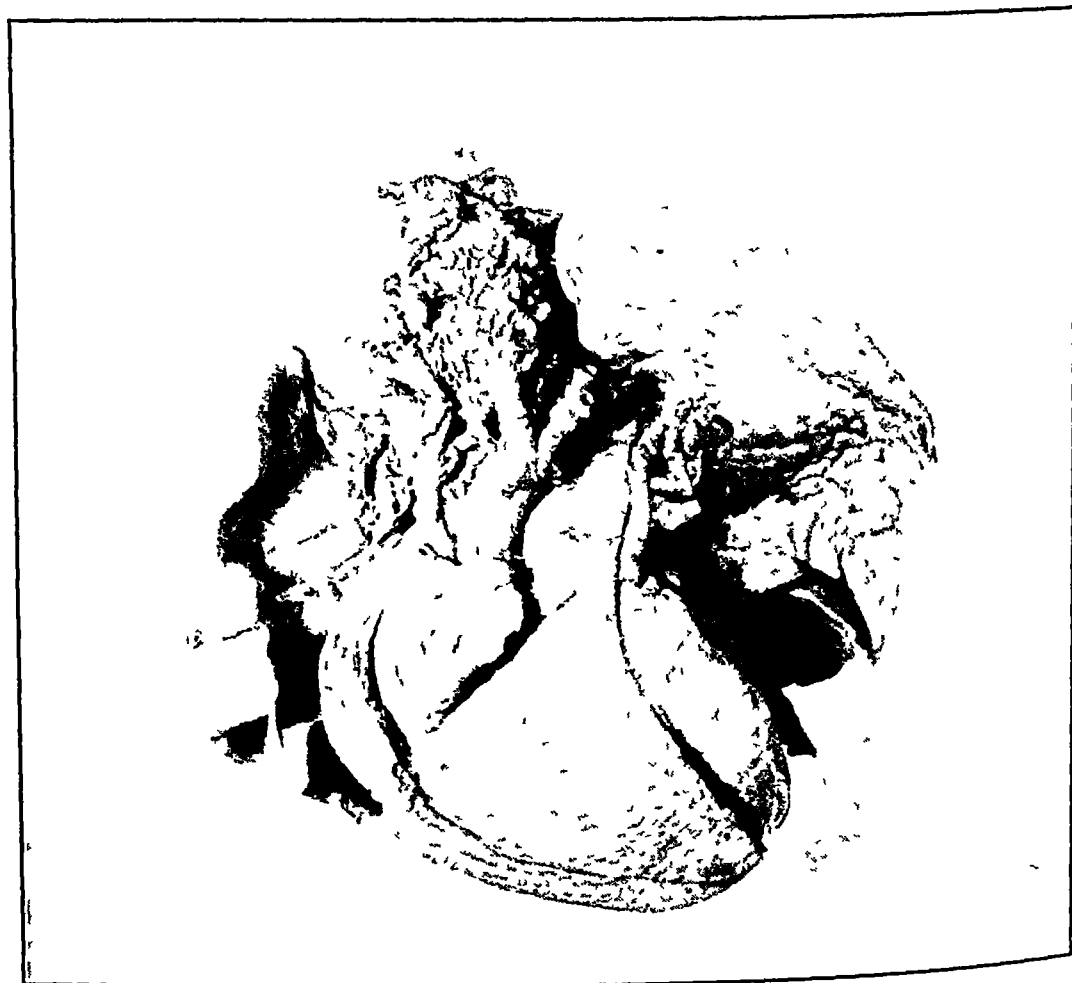
*Pericardium* The wall is not thickened but there is a very definite increase in tension. The sac contains 400 cc of a clear

fluid. In no place is the pericardium adherent to the heart wall.

*Heart* Measures 15 x 11 x 7½ cm. is markedly enlarged. The apex is made up by both ventricles but more so by the right.

*Note* The heart, lungs, and aorta are removed intact and placed in 10% formal. Eight days later a circular dissection was done to observe any abnormal anastomosis of the vessels or any congenital defect which may be present.

*Left Heart* The left ventricular wall measures 14 mm. The musculature appears slightly hypertrophied. No gross areas of fibrosis are noted. The endocardium in the left ventricular cavity is smooth and shining. There is a marked stenosis of the mitral valve with a generalized thickening of the cusps and occasional areas of calcification.



No 5 Lateral view of thoracic organs together with the great branches of the arch as far as the bifurcation Case 2

The ascending portion of the aorta is shown, The much dilated pulmonary artery is shown

fication Only the tip of the forceps can be passed through the opening, the diameter measuring 7 mm In the left auricle the endocardium surrounding the mitral valve is very roughened and deeply congested The left auricular wall averages 3 mm in thickness, and there is a very slight dilatation present The left ventricular cavity is exceptionally small The aortic valve admits the index finger, but the lumen is diminished in size superior to the valve There are three cusps present and the coronary vessels arise from the normal locations

*Right Heart* The right ventricular wall averages 17 mm in thickness, and is markedly hypertrophied No gross areas of fibrosis are noted The endocardium is smooth and shining throughout The tricuspid valve admits three fingers with difficulty, the

edges of the cusps are rolled under and appear slightly thickened, but there is no roughening The right auricle is markedly dilated, with the cavity filled by a large amount of cruor The auricular wall is hypertrophied, measuring 9 mm at its thickest portion The average thickness is 6 mm The pulmonary valve admits three fingers with difficulty, the cusps appear normal The foramen ovale is closed

*Pulmonary Vessels* There is a marked enlargement of the pulmonary artery Superior to the cusps the total diameter is 39 mm with the diameter of the lumen 34 mm Throughout the first portion and the main branches the enlargement is constant The ductus arteriosus is obliterated

*Aorta* This vessel shows a very pronounced hypoplasia throughout its entire

course Superior to the aortic cusps the diameter is 18 mm and at the arch measures 13 mm The size of the vessel remains constant in the descending portion with the diameter at a level of the diaphragm also 13 mm The vessel wall is decreased in thickness, appearing in proportion to the size of the lumen Both iliacs arise from their normal position and are also hypoplastic

All blood vessels are carefully traced and no evidence is found of any anomalous anastomosis The internal mammary artery is not enlarged on either side, the bronchial, pericardial, and esophageal branches follow their normal course

*Lungs* There is atelectasis of the lower lobe on both sides with a marked congestion and edema of the remaining portions

*Thyroid* Does not appear increased in size Only a moderate amount of colloid is present

*Adrenals* Are hypoplastic There is a moderate lipoidosis of the cortex and the medulla appears well preserved

*Female Genitals* The uterus and ovaries appear hypoplastic

#### MICROSCOPIC FINDINGS

*Heart* The left auricle shows marked chronic productive endocarditis with marked fibrosis and areas of active infiltration mostly mononuclear in type Mitral valve shows chronic endocarditis with marked fibrosis and calcification with abundant active infiltrations, both polynuclear and mononuclear Left ventricle shows old sclerosis of endocardium, atrophy of heart muscle with diffuse fatty degenerative infiltration The right auricle shows marked hypertrophy of wall with fatty degenerative infiltration and very small infiltrations in the myocardium, lymphocytic in character The right ventricle shows moderate subepicardial fatty infiltration, hypertrophy of the wall with diffuse fatty degenerative infiltration and small lymphocytic infiltrations There is a slight sclerosis of the endocardium near the tricuspid valve

*Aorta* Markedly hypoplastic Intima shows early stage of atherosclerosis No aortitis

*Lungs* Marked brown induration and chronic passive congestion Bronchioles are dilated Blood vessels show markedly thickened walls with the lumina very small

*Thyroid* Marked lymphoid hyperplasia Graves' constitution Increase of stroma Colloid fairly abundant Parathyroid included shows no pathology

*Thymus* Atrophic, but showing abundant thymic remains Is an atrophic hyperplastic thymus

*Liver* Marked chronic nutmeg liver with beginning central cirrhosis and marked interlobular cirrhosis Proliferation of small bile ducts in islands

*Adrenals* Very hypoplastic with excessive lipoidosis

*Lymph Nodes* Very marked lymphoid hyperplasia Hyperplasia of reticulo-endothelium

*Hemolymph nodes* Show marked congestion of the sinuses, and a most marked lipoidosis of the reticulo-endothelium

*Breasts* Underdeveloped Small ducts resembling male breasts

*Uterus* Slight subepithelial inflammation Endometrium is underdeveloped

*Ovaries* Congestion, cystic follicles, and a small number of corpora fibrosa

#### PATHOLOGICAL DIAGNOSIS

Old sclerosing chronic mitral endocarditis with button-hole stenosis Marked hypoplasia of aorta and iliac arteries Marked dilatation of pulmonary artery Cardiac hypertrophy with right-sided preponderance Dilatation of right heart with relative pulmonary insufficiency Marked brown induration of lungs with areas of atelectasis Marked nutmeg liver with early central and more marked interlobular cirrhosis Extreme congestion of all organs Combined thymico-lymphatic and Graves' constitution (marked lymphoid hyperplasia of thyroid, atrophic hyperplastic thymus, marked hypoplasia of aorta and



No 6 Left ventricle opened showing the stenosis of the mitral orifice Case 2



adrenals, generalized lymphoid hyperplasia with exhaustion of germ centers) Marked hyperplasia of hemolymph nodes with angiectatic blood sinuses and marked lipoidosis of the reticulo-endothelium Chromophobe hyperplasia of the pituitary Hypertrophy of renal glomeruli Hypertrophy of islands of Langerhans

### DISCUSSION

This subject is definitely of the thymico-lymphatic constitution with some added characteristics of the Graves' type The marked hypoplasia of the aorta is a manifestation of her constitution, and there are also present many other of the characteristics common to this group The liver shows a combined cirrhosis, the central cirrhosis is of the Pick's disease type while the interlobular cirrhosis is similar to that found in many of the subjects of the Graves' constitution

The mitral endocarditis appears to be an old rheumatic infection Subsequent to the mitral stenosis and sclerosis of the smaller branches of the pulmonary artery, a marked right ventricular preponderance has developed Cyanosis and polycythemia are manifested in the terminal stages

This polycythemia is definitely compensatory Due to the mitral stenosis and marked sclerosis of the smaller pulmonary vessels normal oxygenation of the blood is prevented Development of the polycythemia is very similar to that in Ayerza's disease where there is a sclerosis of the pulmonary vessels On both occasions in hospital the blood count showed the red cells over seven million, the highest count being 7,900,000

Clinically she showed a definite thyroid disturbance which was aggravated by the administration of "goitric pills" probably containing iodine Microscopic findings prove the thyroid to be of the Graves' constitution type showing the effects of too much iodine

To summarize

1—This is a case of marked hypoplasia of the aorta not associated with any cardiac anomaly

2—She is definitely of the thymico-lymphatic constitution

3—The mitral stenosis is caused by a chronic endocarditis of the rheumatic type

4—Due to poor oxygenation of the blood a compensatory polycythemia develops in the terminal stages

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# A Case of Complete Transposition of the Viscera With Electrocardiographic and X-Ray Studies

By AARON E. PARSONNET, M.D., F.A.C.P. *Attending physician, Beth Israel Hospital, Newark, New Jersey*

**T**RANSPOSITION of the viscera, although not a rare condition, is interesting. Reports of such cases serve a very useful purpose of putting the physician on guard for these anomalies. To the surgeon, and needless to say, to the patient a timely diagnosis of visceral transposition is obviously of the greatest importance.

This case came under my observation through the courtesy of Dr Samuel Roth, of Newark, and holds absolutely true to type as proven by physical findings, electrocardiograms, and X-ray studies.

*History.* L. F. aged 35, well developed, overnourished white male, was seen by me on May 30, 1928, with chief complaint of "pain over heart." Past history discloses nothing of importance, measles and several attacks of tonsillitis were the only diseases of childhood. He always enjoyed good

health and never complained of any symptoms referable to the cardio-vascular or respiratory systems. His father has heart disease at 63, mother living and well at 60.

*Physical Examination.* The apex beat was not visible and not palpable but best heard in the fifth interspace inside nipple line on the right. All heart sounds were clear, well transmitted through entire precordium, regular, and no murmurs, shocks or thrills could be elicited. Orthodiagraphic measurements showed the heart to be of normal size, and fluoroscopic examination revealed the dextrocardia clearly; right and left border configurations were normal in outline. Blood pressure readings were systolic 130, and diastolic 85. The lung fields were essentially clear throughout with definite cardiac dullness over right chest. The spleen could not be palpated on the right but definite liver dullness was present in the left upper quadrant. Under the fluoroscope, typical stomach air bubble seen in right upper abdomen.

The following X-rays were taken on June 6, 1928 --

The electrocardiogram given below shows inversion of the P, QRS, and T waves in the first lead very clearly. All complexes are upright and well formed in second and third leads. These findings are typical of a dextrocardia.

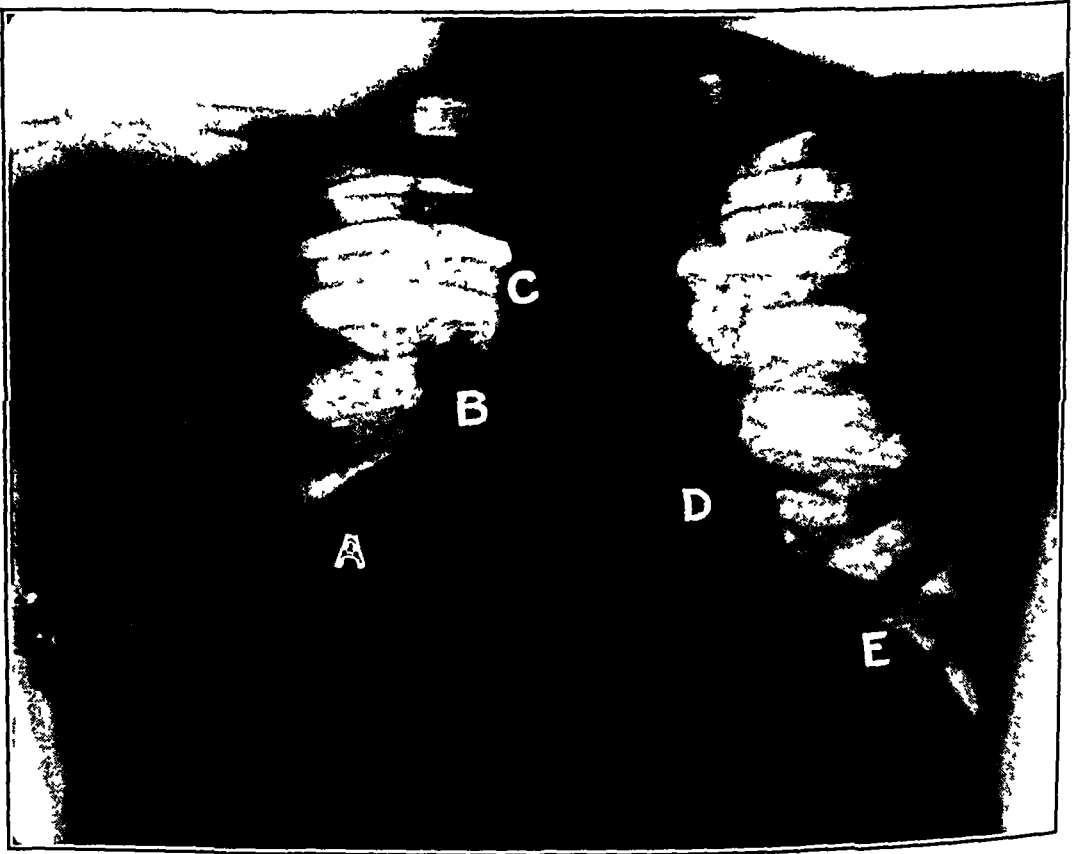


FIG 1 A Left ventricle  
 B Left auriculo-pulmonic curve  
 C Arch of aorta  
 D Right heart  
 E Diaphragm

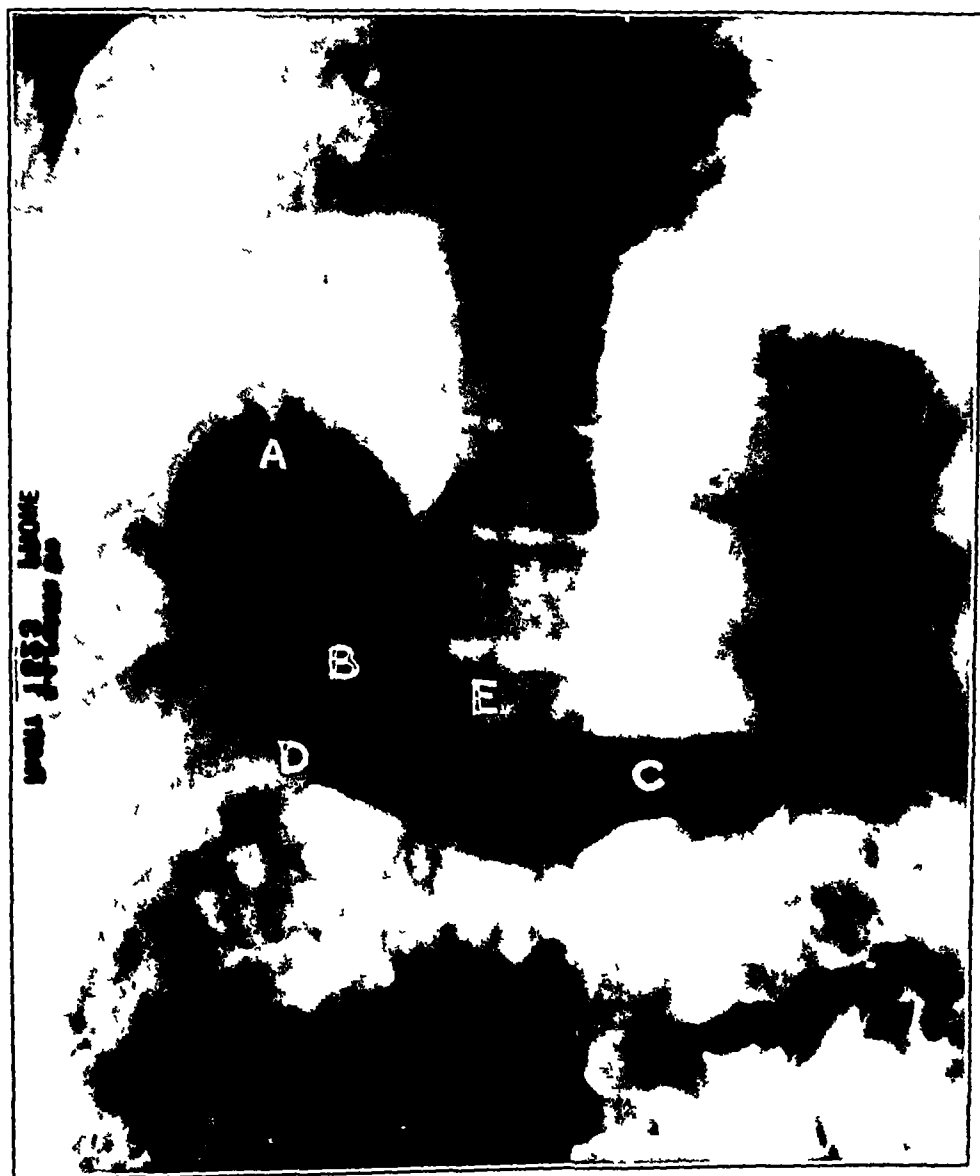


FIG. 2 A Pars cardia  
B Pars media  
C Pars pylorica  
D Greater curvature  
E Lesser curvature



FIG 3 A Caecum  
B Ascending colon  
C Hepatic flexure  
D Transverse colon  
E Splenic flexure  
F Descending colon  
G Sigmoid

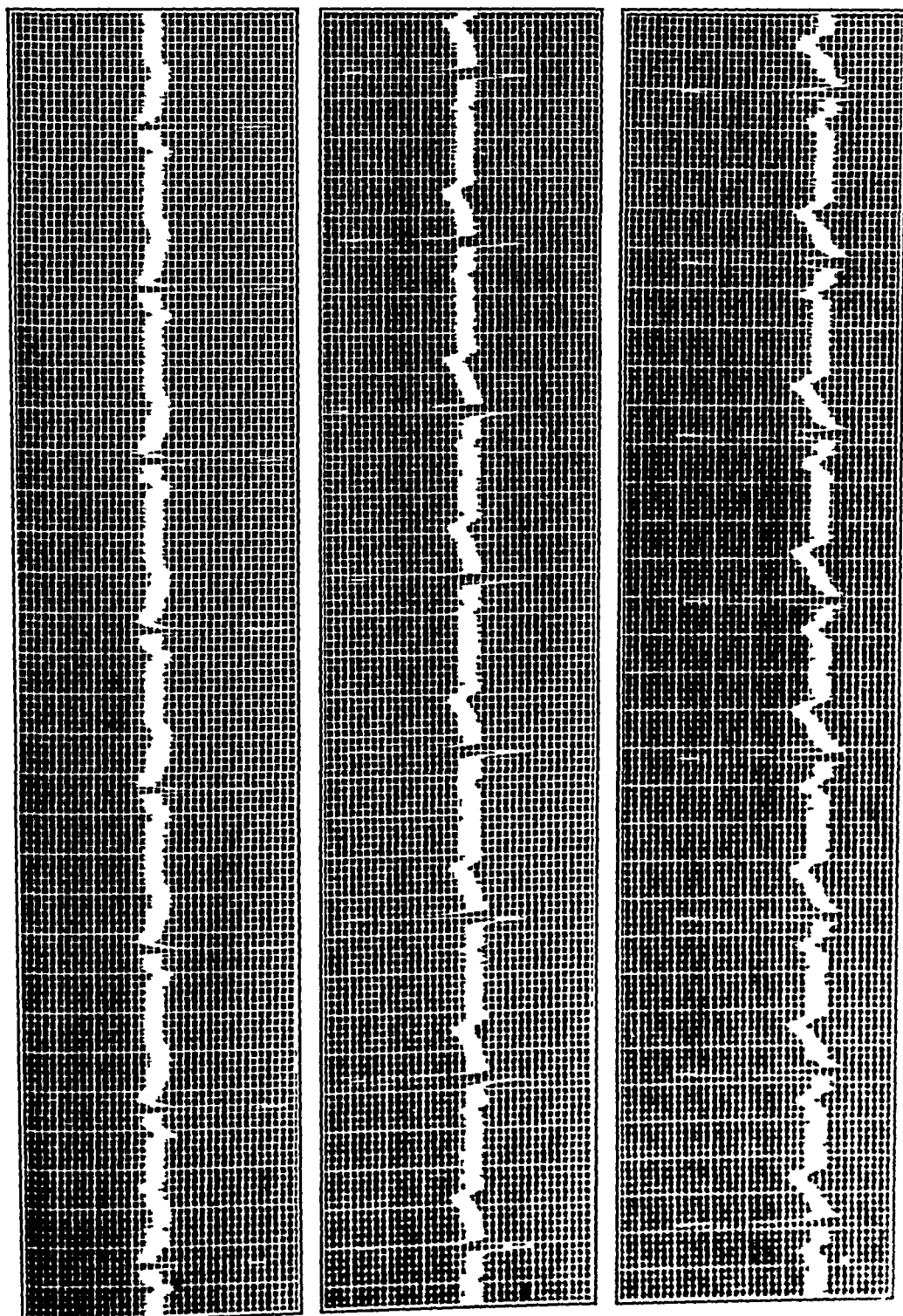


FIG. 1. Electrocardiogram typical of Dextrocardia

# Editorial

## *SYPHILIS AND LIFE INSURANCE*

Karl Vajda of Budapest has an article on "Versicherungsmedizinische Beziehungen der Syphilis" in the number of the *Klinische Wochenschrift* for January 29, 1929, that deserves careful reading and thoughtful attention from every internist who is in any capacity concerned with life insurance examinations. Syphilis has always been one of the most disputed problems of insurance medicine, for two reasons, one, because of the fact that the applicant for insurance, having passed through the active stages of his syphilis, does not mention it to the examiner, and two, because it is extremely difficult often impossible in most cases to make a diagnosis of latent syphilis in the short time allotted to the medical examination. This diagnosis can be much more easily made under the conditions of private practice. In making the insurance examination the examiner has only a relatively short time for his examination so he is forced to omit all methods that may be regarded as burdensome to the candidate. Thus the taking of a Wassermann is attended by difficulties, and a spinal reaction is in the majority of cases not even thought of. Although we have made numerous advances in the diagnosis of syphilis and the discovery of the spirochete,

yet few of these advances are utilized in life insurance examinations to the advantage of the life insurance companies. Syphilis remains today, as it was thirty years ago, one of the most easily missed conditions in life insurance examinations. There is no criterion of complete healing of the disease. A previous syphilis is and remains a menacing danger to life insurance. The latest statistics show that the mortality of leucemics exceeds that of non-leucemics by 68 per cent. This means that for every one hundred cases of death within a given age-class for all insured, there are 168 deaths in leucemics of the same age-class. The examination of the various disease groups shows that the excess mortality of leucemics over that of malignant neoplasms is 60 per cent over that of renal diseases 64 per cent over diseases of the gastrointestinal tract 116 per cent, over suicide 122 per cent, over that of apoplexy 128 per cent, and over that of the group of psychopathic diseases 145 per cent. And this is far from being the whole



than indicated by these statistics. We must not forget in this connection that a candidate with manifest syphilis is never accepted for life insurance. Only such luetic individuals who have had syphilis and have passed through a corresponding treatment for the same and show no symptoms, so that they are regarded by the examiner as completely healed are accepted. Herein lies the greatest feature of the syphilis problem. There is at the present time no doubt existing in any one's mind that the *Spirochaeta pallida* is the cause of syphilis, and although many facts relating to the biology of this organism are still unsettled, we do know that it can reproduce in the human body for many decades without producing any symptoms. During this period of latency the patient may enjoy perfectly sound health, and the physician on the most careful examination can find nothing pathologic. Suddenly in the heart, in the aorta, the central nervous system, in the liver, in the kidney the spirochetes begin their deadly work. Involuntarily we must think of that expression of the great clinician Gerhardt, "Die Syphilis schliesst wohl Waffenstillstand aber niemals Frieden." The great tragedy of it all is that all of these manifestations of this infection are in very many cases diagnosed when all too late for treatment. In the first row stands progressive paralysis as the true horror of life insurance companies. Although the various statistics show that only 2-3 per cent of luetics become paralytic this percentage would hold only for the insurance companies in case every luetic individual would be in-

sured. It is actually much higher among insured luetics, because mental workers rather than laborers fall victims to paralysis. The percentage of cases of progressive paralysis among the insured luetics is 10-12 per cent. Tabes dorsalis is less important than progressive paralysis from the standpoint of the insurance company, in that this form of syphilis leads to death usually only after several decades. Only a few years ago both of these diseases were regarded as meta-luetic or parasymphilitic. Today both are recognized as being nothing else but syphilis of the brain and syphilis of the spinal cord. A similar important role is played by syphilis in the etiology of arteriosclerosis particularly coronary sclerosis, aortic insufficiency, aortic aneurysm, atrophies hepatitis flava, aortitis and myocarditis. Further, there is a large group of diseases to which syphilitics are especially predisposed, such as neurasthenia, gout, diabetes mellitus and cancer. Blaschko has made the observation that he has never seen a cancer of the tongue case that did not have a positive Wassermann. Barsony has called attention to the very high percentage of carcinoma of the uterus occurring in luetic women at the Budapest Frauenklinik. The fearful sequelae of syphilis are well shown in the statistics compiled by Pilz and Mattauschek of 4134 officers of the general army who had acquired syphilis between 1880-1900. These officers had been treated 4-5 weeks with an inunction cure, and thereafter dismissed with a potassium iodide prescription. The following year they were again examined and it signs of

syphilis were still present no one troubled himself as to whether the affected officer should have further treatment or not. The mortality statistics of these officers in the next 12 years showed that 132 died of brain syphilis, 193 of progressive paralysis, 113 of tabes dorsalis, 80 of different psychoses, 17 of aortic aneurysm, 101 of organic heart lesions, 44 of apoplexy, 40 of tertiary syphilis, 147 of pulmonary tuberculosis, and 60 committed suicide. While tuberculosis does not belong to the so-called meta-luetic diseases, it is an old experience that syphilis predisposes to tuberculosis, and that a mild infection often becomes very malignant following an intercurrent infection with syphilis. In the case of those officers who took only one injection cure not less than 23 per cent became paralytic, while of those whose treatment extended over two years only 3.23 per cent developed paralysis, while in those who had a four years' treatment there was not a single case. Eleven years ago Blaschko estimated that there were 40 per cent of the male inhabitants and 19 per cent of the female of the city of Hamburg infected with syphilis, in Berlin 37 per cent male and 17 per cent of the female population. Yet at this time in both of these cities only 3 per cent of the candidates for life insurance acknowledged that they had had the disease. It is easy, therefore, to understand the concern of the life insurance companies in the earlier and more certain diagnosis of latent syphilis. If every luetic candidate for life insurance would acknowledge that he had had the disease, the whole problem becomes reduced to a mat-

ter of financial calculation. Given the excessive mortality rate of the luetic in any age class the increase in premium rate can be easily adjusted. But most of the luetics are silent as to their infection. Some actually do not know that they have had the disease, and some have totally forgotten. There remains, therefore, nothing for the examiner but to make the most painstaking examination possible, many Wassermanns should be taken, and if these are repeatedly negative a bacteriologic and serologic examination of the spinal fluid should be made. But it must not be forgotten that a positive Wassermann does not always indicate syphilis, or that a negative Wassermann does not mean the absence of syphilis. The problem, therefore, cannot be settled in a certain number of cases. It is to be remembered also that very often it is the mildest forms of the disease that terminate in progressive paralysis or tabes. Of great importance in the history are the facts of a childless marriage, or repeated abortions on the part of the wife. Also various conditions of the eye are very suspicious. Syphilis plays a much more important rôle in the etiology of iritis and retinitis than is suspected, a parenchymatous keratitis is probably always syphilitic, likewise chorio-retinitis pigmentosa and optic atrophy. Further of great importance are single neurasthenic disturbances. Since the candidates are always silent as to these subjective symptoms the objective manifestations of the earliest symptoms of progressive paralysis and tabes are of greatest importance. The concentration power of the candidate

should be fully tested, the inability of the incipient case of paralysis to repeat rapidly simple movements of the eyes, tongue and hand should be noted. Here belong also apraxia and dyspraxia, facialis-hypoglossus paresis, tremors of tongue and lips, and above all the pupillary changes. Anisokoria is one of the earliest symptoms occurring many years before the loss of pupillary reflex. The loss of the pupil reflex is in 98 per cent of cases a symptom of tabes or paralysis. In concluding his observations Vajda states that after 4-5 years of scientific treatment insurance may be given a luetic without especial increase of premium. But the number of such candidates is so very small compared to those imperfectly treated that the greatest care must be taken in regard to the latter class. In this group he would give no insurance to any one with active clinical symptoms until perfectly treated. A half year after the end of such treatment in the total absence of symptoms insurance for a period of 15-20 years can be given at normal premium rates. After that period insurance can be continued at a small increase of premium. In case there are no symptoms and the candidate has been well treated without symptoms for the last two years, he may be accepted at normal rates for 15-20 years if five years has passed since the infection. If ten years have elapsed since the infection then a slight increase of the premium is justified. Because of the action of the International Serum Conference in regard to the evaluation of the negative and positive Wassermann reaction

Vajda can no longer support the views of v. d. Berghs that in the case of a negative Wassermann in the candidate for life insurance a small increase of premium should be made, and in the case of a positive reaction a greater increase in the premium rate.

### THE MEETING IN BOSTON

From the large number of letters coming in to the Editor's office it would seem that a large attendance is already assured for the Boston Clinical Week. This augurs most promisingly for the success of this meeting. The Boston men have prepared a fine program. Especially attractive is the clinical program which ensures a high grade of clinics suitable for the postgraduate. Attention has been given to the criticisms of the clinics presented at the last two Clinical Weeks to the effect that these clinics were of an order suitable to senior students but not of a postgraduate quality and flavor. The medical visitor to Boston may be assured that all of the clinics presented there are by trained clinicians who have had postgraduate experience and that the material and the presentation will be worthy of the reputation for high-class postgraduate work which Boston has always enjoyed. In addition to those given by the local men clinics will be presented by members of the College from other cities, whose reputation for giving postgraduate work of the highest class is well-known. As far as the medical value of the Boston Clinical Week is concerned its success is assured through its program. It behooves the Fellows to

Associates of the College to take advantage of this opportunity for social and intellectual refreshment. As to the other aspects of the meeting in Boston very little can be said in addition to what the special articles on Boston already published in the College News Notes have offered. The historic interest of the city is so great, so interwoven with the history of America, that the visitor to Boston for the first time will have his time wholly filled for him if he does nothing but visit the great historic buildings and scenes which make of the city such a unique object lesson for early American history. The city portion of Boston with its mingling of historic buildings and business blocks has an English atmosphere—the vis-

itor may easily fancy himself to be in London in some of the vistas seen through narrow passage-ways and streets. To the acquainted visitor the art collections of Boston offer much, to the botanist and gardener the Arnold Arboretum is an unfailing joy and interest; to the musician the opportunity for hearing the Orchestra is an enticement, for the educator there is Harvard and the Institute, for the book-lover there is the Widener collection, in fact Boston offers something especially choice in every line of human interest. So then, come to Boston, and plan to take advantage of the many great opportunities, both medical and cultural, that the holding of the Clinical Week in this interesting city makes available to you.

## Abstracts

*Syphilitic Heart Disease with Failure* By DUDLEY C SMITH and RAYMOND D KIMBROUGH (The Southern Medical Journal, August, 1928, page 634)

This analysis is based on the study of fifty-six cases admitted to the University of Virginia Hospital between July, 1923 and July, 1927. All of the cases had heart failure and were diagnosed syphilis of the heart or aorta. Syphilis was considered the primary etiological factor, this was proved by autopsy in some of the cases, but in most of them the diagnosis was based on clinical and laboratory data. The cases of heart disease showing what was considered an incidental syphilitic infection and those in which it was thought to be of secondary importance were discarded. In addition to the usual medical investigation consisting of history, physical examination and routine laboratory methods thirty-four of the patients had electrocardiograms, forty-two were X-rayed and eight were autopsied. Of the fifty-six cases, thirty-nine (69.6 per cent) were negroes, and seventeen (30.4 per cent) were whites. The proportion of negro syphilitic patients to white syphilitic patients in the hospital and out-patient departments was 3 to 2. From these figures it is estimated that syphilitic heart disease occurred one and one-half times as frequently in syphilitic negroes as in syphilitic whites. The average age of the negro patients in this group of admission was 45.8 years as compared with 52.6 years for the white patients. The greater incidence and the earlier occurrence in the negro indicates an increased susceptibility in this race to cardiovascular involvement from syphilis. There were forty-nine male and seven female patients. Fourteen were farmers twenty were laborers and the occupations of all the others required considerable physical exertion. The average age at admission was 47.7 years. There was a positive history of

a genital sore in twenty-five cases. The average interval in these from the initial infection to the onset of failure was twenty-two years. The shortest interval was eight years, the longest forty-one years. Only one case gave a history of early cutaneous lesions. This would seem to confirm the idea expressed by Brown and Pearce in their law of inverse proportion, that severe late visceral involvement occurs more often following mild early reactions. This finding is paralleled by the well substantiated observation that neurosyphilis is relatively less frequent in those patients who have had severe skin symptoms. It is impossible to say whether this is due to different strains of organisms, or to an individual visceral susceptibility. Tabulation of the initial symptoms gave the following results: dyspnea 29 (51 per cent), heart pain 10 (18 per cent), palpitation 10 (18 per cent), substernal pain 3 (5 per cent), weakness 3 (5 per cent), cough 2 (4 per cent), vertigo 2 (4 per cent), headache 1 (2 per cent) and dyspepsia 1 (2 per cent). Some showed more than one initial symptom. Other early symptoms were: edema 28 (50 per cent), dyspnea 14 (25 per cent), heart pain 12 (21 per cent), cough 12 (21 per cent), palpitation 11 (20 per cent), vertigo 10 (18 per cent), weakness 9 (16 per cent), substernal pain 4 (7 per cent), dyspepsia 3 (5 per cent), choking sensation 3 (4 per cent), nervousness 2 (4 per cent), sleep starts 2 (4 per cent), headaches, convulsions, insomnia, cyanosis, hoarseness and buzzing sound in heart 1 each. Functionally twenty-five cases presented both congestive and anginal failure, thirty showed congestive failure alone and one anginal failure alone. The abnormal structural findings based on physical examination, electrocardiograms, fluoroscopic examination and autopsies were as follows: cardiac hypertrophy 51 (91 per cent), pericarditis

tation 33 (59 per cent), dilated aorta 31 (55 per cent), aneurysm of the aorta 18 (32 per cent), myocarditis 3 (5 per cent), and coronary occlusion 1 (2 per cent). In three of the eight autopsies marked fibrosis and degenerative myocarditis was noted. These were the findings in routine post mortem examinations, and it is probable that microscopical studies would have revealed other instances of specific myocardial changes. Forty-nine of the fifty-six cases had positive blood Wassermann reactions, a percentage of 87.5. Of the remaining seven cases syphilis was evinced by other conclusive findings. Twenty-six of this group had spinal fluid examinations. There were normal findings in fourteen of these tested in twelve instances, or 46 per cent of those examined, there was positive evidence of central nervous system involvement. The positive spinal fluid findings were the means of confirming syphilis as the etiological factor in some of the cases with negative history and negative blood Wassermann. The average blood pressure in the thirty-three cases of aortic regurgitation was systolic 150, diastolic 60, pulse pressure 81. Case without aortic regurgitation showed systolic 138, diastolic 80 and a pulse pressure of 58. The average blood pressure in all cases was systolic 145, diastolic 74, giving a pulse pressure of 71. The thirty-four electrocardiographic tracings revealed nothing distinctive. Left axis deviation was present in most cases as might be expected in left cardiac hypertrophy. Five patients had partial or complete heart block. The forty-two roentgenographic examinations proved the value of this procedure in determining the structural abnormalities in the heart and aorta. Several cases with negative physical examination showed definite changes such as aneurysm or dilated aorta on examination. This method of examination was also valuable in differential diagnosis from an etiologic standpoint. Forty-eight of the fifty-six cases gave no history of antisyphilitic treatment. The remaining eight gave a history of 'internal' treatment, probably mercury and iodids. Most of the cases in which a history of initial infection was obtained began before the modern era of

antisyphilitic treatment. The few cases that acquired their infection since the discovery of arsphenamin gave no history of intravenous treatment. Twenty-one of the fifty-six cases are known to be dead, eighteen are known to be alive and the condition of seventeen is unknown. Of the eighteen alive, thirteen are improved and five unimproved. In the group of twenty-one which are dead the average interval from the onset of failure to death was 3.2 years. The average interval since onset of failure in those alive and heard from is 4.1 years. There is undoubtedly a factor in certain of the cases which accounts for a more rapid progression of the heart deficiency, but it has not been determined in this study. In summarizing, these authors find that syphilis is an important etiological factor in heart disease especially in the southern states. The prevention of syphilis will eliminate this group of cardiovascular disorders. The findings in fifty-six cases of syphilitic heart disease with failure are in part presented. The negro race in this country is probably more susceptible to syphilitic heart disease than the white race. Only one in the group of fifty-six cases gave a history of early cutaneous involvement.

*Über das Auftreten von temporärem Hyperthyroidismus während der Insulinkur*  
By F. HOGLER (Klin. Wochenschr., January 29, 1929)

Hogler reports two cases in which the insulin cure was interrupted because of the appearance of a temporary hyperthyroidism, with symptoms of tachycardia, fine tremors, damp skin and maniacal condition of excitement with an increased basal metabolism. After the cessation of the insulin the hyperthyroid symptoms disappeared and the basal metabolism fell to the normal. The production of the basedowian symptoms through insulin points to a correlation between the thyroid and islands of Langerhans. Even under normal conditions may any overproduction of insulin produce a certain increased activity on the part of the thyroid. One may suppose that with very labile thyroid function the thyroid will respond to this stimulation in an abnormal manner thereby increasing the increase of assimilation due to

sulin. These observations gave rise to the thought that constitutional leanness might have its origin in an abnormal interaction between thyroid and island-apparatus, in that every exogenous or endogenous increase of insulin could lead to an opposing abnormal increased thyreogenic regulation. Observations made upon the action of insulin in cases of the asthenic type did not, however produce any increase in the basal metabolism or give rise to any basedowian symptoms.

*Effect of an Exclusive Meat Diet on Chemical Constituents of the Blood* By CLARENCE W. LIEB and EDWARD TOLSTOI (Proc of the Soc f Exper Biol and Med, January, 1929, page 324)

This is a preliminary report of an experiment to study the effect on human beings of an exclusive meat diet of several months duration. The subjects were two Arctic explorers who had spent many years in the Arctic Circle and while there, had lived for the greater part of the time on a practically 100 per cent meat and fat diet. Preliminary to this study they were given careful physical examinations. Both were in excellent condition and shared no evidence of impaired health. Following those examinations studies were made of the respiratory exchange, ketogenesis, protein balance mineral metabolism fecal bacteriology, hematology and blood chemistry. This report confines itself to the blood chemical findings. Both men ate nothing but meat, cooked or raw. Two experienced dietitians prepared and served the meat. No subjective untoward effects were noted. One of the subjects at one time developed nausea and diarrhea while on a lean meat diet, the other suffered from an incidental attack of influenza of 3-4 days duration with uneventful recovery. Each subject consumed 120-130 gms of protein and enough fat to total a daily caloric intake of 2200 to 2800. Both men were up and about and took their exercise in walking. At times when they left the hospital they were accompanied by an attendant so that there might be no criticism as to the supervision of their diet. After 4 months the intensive metabolic studies were temporarily suspended. These

subjects reported once a month for blood chemical studies which were continued for a period of 11 months. The communication deals with two questions. 1, Does an exclusive meat diet over a period of 11 months affect the kidneys? 2, What changes, if any, are found in the blood of men receiving such a diet over the period mentioned? The following were studied: N P N, urea, uric acid, creatinine, NaCl, sugar, CO<sub>2</sub> CP, serum Ca, plasma P, albumin (plasma) globulins, total protein (plasma) A/G, and cholesterol, before the meat diet and after an exclusive meat diet for eight months. All analyses were done in duplicate whenever there was a question as to the correctness of the procedures; analyses were checked at frequent intervals. The data may be summarized as follows: (1) two healthy men, living exclusively on meat diet for the past 11 months, felt no untoward effects, maintained their weight and were in excellent health; (2) no evidence of renal impairment was found; (3) the chemical composition of the blood is little affected except for a slight increase in uric acid and a temporary lipemia. The latter occurred significantly only after unusual amounts of fat had been taken.

*Morbus Basedowii und Perniciöse Anämie* By E. MEULINGRACHT (Klin Wochenschr, January 1, 1929)

During the last several years Meulengracht has been convinced through a series of observations that a certain connection exists between exophthalmic goiter and pernicious anemia, in that a number of cases exceeding pure coincidence of pernicious anemia has been seen to develop in individuals that earlier in life had suffered or were still suffering, from Graves disease. In the course of the last year he has seen eight cases of pernicious anemia developing in patients with exophthalmic goiter. These patients were all women. It appeared also that in these symptoms of pernicious anemia developed earlier in life than ordinary. The cases of Graves disease appeared to be of medium severity and were not distinguished in any way from other cases of the same disease. In some patients the disease developed slowly and after the attacks of a

of the pernicious anemia, either no Graves' symptoms or only mild signs of the disease were present. In some cases a hereditary tendency to pernicious anemia was present in the family, in others no history of a family incidence was obtainable. Two departures in symptoms were noted in the cases, all of these patients were very thin, and in some of the cases marked pigmentation of the skin occurred. Both of these symptoms were referred to the previous Graves' disease. Otherwise the picture presented by the pernicious anemia was the usual one of glossitis, acroparesthesias and achylia. In some of the patients the achylia preceded the anemia by several years, even during the Graves' symptoms. The hematologic picture was the classic one, and the patients reacted characteristically to liver diet. In all of the cases symptoms of Graves' disease preceded those of pernicious anemia, the time period between the two conditions varying from 7 to 28 years. What is the explanation for the occurrence of the two diseases in the same individual? Because of the relative rarity of the two conditions Meulengracht excludes the possibility of the association being purely one of coincidence. The possible action of roentgen treatment is ruled out, since this treatment had been used only in a few of the patients. That the anemia might be the result of a secondary hypothyroidism seems also ruled out by the fact that none of the patients showed any signs of a hypothyroidism, and by the further fact that the basal metabolism in those cases in which it was determined was normal or slightly raised. Further the good results obtained by the liver treatment decided against the diagnosis of myxedema. According to Meulengracht's conception of the cases two possibilities present themselves: 1, that the pernicious anemia developed on the basis of an achylia due to the hyperthyroidism; 2 that in hereditary-biologic connection exists between the two conditions. It is well known that Graves' disease in a large number of cases is accompanied by achylia. Since achylia in general has the pathogenesis of pernicious anemia it is expected that patient surviving

Graves' disease would show a tendency to the development of pernicious anemia. On the other hand both Graves' disease and pernicious anemia show a marked tendency to be hereditary, and certain factors in the genotype must be of significance for the development of both diseases. There lies the possibility that a relationship exists between the hereditary factors concerned, and that the two diseases may, therefore, on this ground show a tendency to occur in the same individuals and in the same families. Meulengracht is convinced that a relationship exists between the two diseases.

*Ueber die Aktivierung des Insulins bei Nicht-diabetischen.* By E. Vogt (Klin Wochenschrift, July, 1928, p 1460)

By activation of insulin one understands a strengthening and a prolongation of its antidiabetic effect through different means. Bertram mixed insulin with albumin bodies, with caseosan and human serum. The intramuscular injection of the mixture produced in diabetic and in normal rabbits a definite strengthening and prolongation of the lowering of the blood sugar. In further experiments Vogt has produced similar results through the injection of aolan and novoprotein. The most marked effect was produced through the use of the diabetic's own serum. Very important is the fact that the activation occurs only in intramuscular injections, but not after intravenous. Bertram regarded the activation as due to a change in the resorption condition of the insulin. Vogt experimented on non-diabetic women who had recently undergone a fasting cure, adding serum to the insulin. The experiments were carried out at all stages of the sexual cycle. The addition of serum to the insulin gave weakest results when taken at the close of menstruation. From the middle of the intermenstrual period the serum possessed a definite activating power. The high point of activation was reached regularly one or two days before menstruation began. During menstruation the serum showed a lowered activating power. From these investigations it can be seen on non-diabetic women that the activation of their reproductive activity is associated with the activity of insulin.



maximally by the addition of serum taken just before menstruation and possessing the highest content of the female sexual hormone. The addition of the female albumin-free sex-hormone folliculin influences the action of insulin in a similar way. On the contrary the serum after operative castration or roentgen castration has only a very slight activating power. The irradiation of insulin with the artificial Alpine light or

with the roentgen carcinoma dose produces also a definite activation of the insulin. These findings possess a theoretical interest but possibly also a practical application. It would be a step forward in the insulin therapy of diabetes to be able to use smaller doses of insulin to obtain a given effect when the high price of insulin preparations is taken into consideration.



method At the Laboratory Conference on the Serodiagnosis of Syphilis, arranged by the League of Nations Health Committee, held in Copenhagen, May 21 to June 4, 1928, 957 sera were examined by Dr Kahn in comparison with 13 other methods About half of these sera came from patients suffering from diseases other than syphilis (tuberculosis, gonorrhea, cancer, etc) The Kahn Test gave no false positive reactions Experience gained with over 500,000 Kahn tests indicates that this method is highly specific for syphilis The author is, however, conservative and very wise in his statement that *no laboratory method should be accepted by physicians as the final criterion in the diagnosis of any disease without due regard to clinical manifestations* A positive (++++, ++, or ++) Kahn reaction should be taken as a very strong indication of syphilitic infection A very weak (+ or  $\pm$ ) reaction should be taken as a lesser probability A negative Kahn reaction is an indication of the absence of syphilis It should be emphasized, however, in spite of the fact that the Kahn test is more sensitive than practically all other serological methods, that a negative reaction does not entirely eliminate the possibility of syphilitic infection The book is especially to be recommended for its very clear concise style, and conservative presentation

*What Is Life?* By AUGUSTA GASKELL Introduction by KARL T COMPTON, Professor of Physics, Princeton University, and RAYMOND PEARL, Professor of Biology, The Johns Hopkins University 324 pages Index of 1527 references Charles C Thomas, Springfield, Illinois—Baltimore Maryland, 1928 Price in cloth \$3.50 net

According to this new theory of life, living matter *invariably* consists of an atomic system (a system made up of chemical atoms) that is organized and interpenetrated by another system The atomic system is matter, or a material system, the intraatomic system is life, not matter, immaterial The two systems are constituted of the same kind of ultimate units (positive and negative electrons) but are built on different patterns The structure of liv-

ing matter *invariably* shows this dual pattern *Living matter, then, invariably is a dual system, the constitution (or pattern) of which is partly material and partly immaterial, the presence of the immaterial system within the material system constituting the living state* Since "uniform relations" constitute a "law," the expression of this fact, then, is a statement of *the law of the structure of living matter*, and this law of the structure of living matter defines the difference between *inert* and *living*, and between *living* and *dead* organisms *Life is a quantity*, it is not matter and is unlike matter Life consists of *the same constituent units* as does matter, and represents a manner of combination of ultimate units different from the pattern of their combination to form the chemical atoms, or matter In the living organism, life is an intraatomic quantity This definition of life applies to *all* life-forms without exception That which sometimes has been described vaguely as "the life-principle," that which determines the living state (or the state of living), whether of plants or animals, or of man, *alike in all*, is the intraatomic quantity "life." Life forms a definite series, different from the series that from atomic number 1 to atomic number 92, is matter All life-forms are alike basically in that, or in so far as, life is owing to a peculiar manner of the combination of ultimate units The differences between one form and another form are determined quantitatively, but there is *no arithmetical progression* (as in the elements), a very large number of different forms and variations of forms being possible Specific and different properties necessarily characterize the combination of ultimate units after a pattern unlike that of the chemical atoms, or matter, *the peculiar manner of combination that spells life, giving rise to the peculiar properties of life* Since *all psychic properties attend life* and life defined as a quantity it follows that the quantity 'life' is identical with 'soul' Life and the soul are not, as some have insisted two different problems, nor is the problem of "mind separate from the problem of life All problems of the soul and

of the mind are problems of the quantity "life." According to the theory, death of an organism can mean only one thing—the rupture between and the separation of the two systems that constitute the organism. The preceding quotations will sufficiently show the nature of Mrs Gaskell's argument for the dual nature of the living organism. Her hypothesis is in essential the translation of very primitive conceptions of the body and soul relationship into the language of modern physical chemistry and biology. In truth, one finds nothing more here than the concept of man with a body created out of the dust of the earth into which the breath of life has been breathed, rendered in the scientific jargon of the chemistry, physics and biology of the times. As Compton wisely says in his preface that the honest physicist must admit that he knows no independent experimental evidence to suggest or support the hypothesis of these assumed "Z" combinations of protons and electrons, and he must admit further that he really knows relatively very little about atoms, protons and electrons, and nothing at all about the explanation of life. The decisive proof of Gaskell's theory would involve the proof or disproof of the existence in living matter of combinations of protons and electrons in a different unit structure from the ordinary atoms of the inorganic world. There exists the possibility that her theory can be used as a working hypothesis and that it should be susceptible of experimental proof. Aside from its unproved hypothesis, this book is interesting and stimulating for the concise review of modern physical chemistry and biology given in it. It is a very good example of a hypothesis developed and extended to far-reaching proportions, without a single supporting physico-chemical fact, interesting but unproved. The book is very well printed, and attractive in its format.

*The Diabetic Life Its Control by Diet and Insulin*. A Concise Practical Manual for Practitioners and Patients. By R D LAWRENCE, M A, M D, M R C P (London), Chemical Pathologist and Lecturer in Chemical Pathology, King's College Hospital. Fourth Edition. 188 pages, 12

illustrations. P. Blakiston's Son & Co, Philadelphia. Price in cloth \$2 50.

Each year since 1925 has seen a new edition of the exceedingly practical little book on the diabetic life. In the one just passed since the last edition there have been advanced no revolutionary ideas on the use of insulin or the treatment of diabetes. More practical details, however, have been incorporated in this volume, and fuller information is offered on the treatment of coma and intercurrent illnesses, since these constitute the most difficult and dangerous problems which the treatment of diabetes presents. Great changes have been made in the tables of food values for carbohydrates, as the result of extensive analyses carried out by the author in association with McCance during the last three years. They discovered that many carbohydrate foods, especially green vegetables, contain much less starch and sugar than formerly supposed. This means that diabetics using their food tables will be allowed larger quantities of some vegetables and fruits than before, and may need in consequence a few more units of insulin a day. It also means that more uniformly accurate dietetic work will be possible, and this is certainly of great importance in experimental work, such as testing new diabetic remedies. This little manual presents the essential facts of the treatment of diabetes in simple concise statements intelligible to both practitioner and layman.

*Fistula of the Anus and Rectum*. By CHARLES JOHN DRUECK, M D, F A C S, Professor of Rectal Diseases Post Graduate Hospital and Medical School, Chicago, Illinois. 318 pages, 66 original illustrations. F A Davis Company, Philadelphia, 1927. Price in cloth \$3 50 net.

Every practitioner is called upon to treat patients suffering from rectal fistulae, and many times finds himself confronted by a confusing array of symptoms with which he is unable to cope. Little is taught in our medical schools in regard to the subject, and there are numerous and diversified opinions as to both etiology and treatment. In the presentation of this monograph the author has put together the ana-

tomical, pathological, physiological and clinical knowledge gained through years of study of a large number of cases that had been required to submit to more than one surgical operation, and, even then, went on uncomfortably through life. In the treatment of rectal fistulae the physician must remember that the technical procedures incident to the removal of the fistula are only the first steps in the treatment, and that he must always preserve the functions of the rectum and anus. In a region the anatomy of which is so complicated and intricate as the perineum, the preservation of function becomes a complicated problem. Any one may introduce a director through a fistula into the rectum and rip up the overlying structures, but the carefully planned procedure which preserves vital tissues, even though the sinus goes through or around them, reflects credit on the surgeon. No matter how complicated the fistula, the functions of the sphincters, levator ani, and the important nerve and blood vessel trunks must be preserved. The technical methods used in bringing about successful results in the treatment of rectal fistulae are given in careful detail in this book. It represents a very thorough and careful presentation of the subject.

*Diseases of the Blood* By A. PINEY, M.D., M.R.C.P., Research Pathologist, Cancer Hospital, London. 195 pages, 20 illustrations, six in color. P. Blakiston's Sons & Company, Philadelphia, 1928. Price in cloth, \$4.00.

The author thinks that, while it may seem that little excuse exists for the publication of yet another book on the blood, there is no other book that covers quite the same ground as the present one. The student does not, as a rule, want much hematologic detail, and the practitioner only requires bare outlines of immediate practical value. The present book is an attempt to supply such information. It is hoped that it will also serve as an introduction to more detailed treatises which often fail in their intention by presuming that the reader is already acquainted with the more elementary aspects of hematology. In spite of the predominantly practical na-

ture of this book, it has been thought necessary to devote rather more space than is usual to a consideration of the underlying anatomical changes in the hemopoietic organs, because without some knowledge of these, it is impossible to obtain the maximum of information from the blood picture. Following an introduction, the various chapters treat in succession of leukocytic variations, erythrocytic variations, leukemia, diseases allied to the leukoses, myelomas, some forms of anemia, anemias of childhood, hemorrhagic diathesis, polycythemia, forms of splenomegaly and symptomatic blood changes. Following these there is an appendix treating of hematologic technique, blood groups and blood transfusion, and X-rays and radio-active substances. A useful glossary completes the book. This little book is as much up to date as any text book can be, particularly in reference to the pathologic anatomy underlying the hematologic changes. It is by far the most practical work on hematology that the reviewer knows of, it is highly to be recommended to the medical student and the practitioner. The latter will find in it an excellent resume of the clinical symptoms, as well as of the known pathology of each of the known hematologic conditions, with a sufficient consideration of their treatment.

*Clinical Physiology (A Symptom Analysis) In Relation to Modern Diagnosis and Treatment*. A Text for Practitioners and Senior Students of Medicine. By ROBERT JOHN STEWART McDOWALL, D.Sc., M.B., F.R.C.P. (Edin.), Professor of Physiology, King's College, University of London. With an Introduction by W. D. HALLIBURTON, LL.D., F.R.C.P., F.R.S., Emeritus Professor of Physiology, King's College University of London. 383 pages, four plates. D. Appleton and Company, New York. 1927. Price in cloth \$3.50.

This volume is an attempt to present some of the facts of Physiology and their applications in General Medicine in a form which fits in conveniently with pathological and clinical teaching. This has been made necessary a complete departure from the usual arrangement of physiological text-

book, and it will be realized that it is not easy to collect material over such a wide and varied field and yet to keep the volume within easily readable limits. The book is intended primarily for senior students and practitioners of medicine who are too busy to read more exhaustive monographs, but who are nevertheless anxious to familiarize themselves with the physiological principles upon which so many of our modern methods of diagnosis and treatment are based. The author's experience as a teacher of clinical medicine gave him an opportunity to study in some detail how far the average medical student was able to adapt his knowledge of the science of physiology to his practical requirements. While it was fully realized that the study of Physiology in its more scientific aspect was in every way desirable, it was clearly seen that for the adequate appreciation of the signs and symptoms of disease more was necessary than is usually taught by the physiologist or clinician. For example, it is extremely difficult, indeed almost impossible from the study of ordinary text book physiology, for the student to see why a cardinal sign of cardiac disease should be breathlessness. This is a textbook then of applied or bedside physiology, and is of great value as a practical correlating branch of study, especially for medical seniors and internes. It achieves its object very successfully, and is to be recommended for senior reading.

*A Manual of Materia Medica For Medical Students* By E. QUIN THORNTON, M.D., Assistant Professor of Materia Medica in the Jefferson Medical College. Second Edition, Thoroughly Revised. 384 pages. Lea and Febiger, Philadelphia, 1927. Price in cloth \$4.00.

The tenth decennial revision of the United States Pharmacopoeia became effective on January 1, 1928. Among many other changes in that book, there were 40 pharmacopoeial articles added, 191 deleted and 47 official titles changed. On account of these extensive changes it became necessary to revise this manual, and the author has taken advantage of this opportunity to condense, rearrange and practically rewrite

it. An object constantly kept in view has been to arrange and condense the text so that all articles of the United States Pharmacopoeia might be lectured upon by the teacher, and studied by the student within the hours devoted to the subject of materia medica during the college year. The book is divided into three parts. In Part I a limited number of pages are devoted to Posology, Methods of Administering Drugs, Common Incompatibilities, Weights and Measures and the Latin Language as applied to Prescription Writing. Part II discusses Inorganic Articles of the Pharmacopoeia arranged in closely allied groups. Part III includes all Organic Official Substances arranged according to their most common uses. The author assumes that it is of little value for medical students to know the botanical origins or the minute structure of roots, leaves, etc., or know the method of manufacturing chemicals, but he believes it of prime importance for them to know Latin and English names and synonyms, the general appearances and characters of drugs and remedies, important constituents, percentage strengths of heroic remedies, composition of the compound galenical preparations, common incompatibilities, methods of administering and doses of all pharmacopoeial drugs. This volume is an eminently practical exposition of the ground covered by it, it represents a concise and careful condensation of materia medica knowledge, freed from unnecessary extraneous material.

*René Theophile Hyacinthe Lacnec A Memoir* By GERALD B. WEBB, M.D., President, Colorado School of Tuberculosis, Colorado Springs, U. S. Government Delegate to the Laennec Centenary, Paris, December, 1926. 146 pages, 13 full-page plates. Paul B. Hoeber, Inc., New York, 1929. Price in cloth \$2.00. Special Edition of 120 copies on Kelm-scott Hand-made paper, with illustration on Japanese Vellum, signed by the author \$12.50.

Heretofore there has been no attempt to give a complete picture in the English language of the immortal French physician Laennec, and to few outside of the medical

profession is his name known. The present volume is the result of an address given by Webb before the Denver Clinical and Pathological Society on February 9, 1926, in commemoration of the centenary of the death of Laënnec. Rewritten and elaborated for publication that address appears in the form of the present volume. In it Webb sketches in a thoroughly delightful manner the story of Laennec's birth and family, his boyhood and school life, the period of his medical study at Nantes and in Paris, the entrance into practice and teaching, and his discovery of the stethoscope. In August, 1819, there appeared his monumental work "*De l'Auscultation Médiate, ou Traité du Diagnostic des Maladies des Poumons et du Cœur, fondé principalement sur ce nouveau moyen d'Exploration*," which met the usual harsh reception

given to works of genius on first appearance, especially in his own country, although well received elsewhere. The story continues with descriptions of his illness, return to Paris and the rather pathetic events of his last days. Throughout this interesting biography the author reveals his intensive admiration for, and deep sympathy with his subject, whose name remains one of the greatest in the history of tuberculosis. It is a well-told biography, the essential facts are all there, with a sufficient background of atmosphere. The interesting illustrations are for the most part taken from the volumes on Laennec published in 1912 and 1920 by Alfred Rouveau. This volume is another one of Hoeber's little achievements in the field of medical history which should be in the possession of every man interested in the medical life

# College News Notes

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## PROGRAM THIRTEENTH ANNUAL CLINICAL SESSION

### BOSTON COMMITTEES

JAMES H. MEANS, *General Chairman*

### COMMITTEE ON ARRANGEMENTS

JAMES H. MEANS

WILLIAM B. BREED

HENRY A. CHRISTIAN

RANDALL CLIFFORD

CHESTER M. JONES

ELLIOTT P. JOSLIN

ROGER I. LEE

GEORGE R. MINOT

JOHN H. MUSSER

JOHN PHILLIPS

JOSEPH H. PRATT

FRITZ B. TALBOT

CONRAD WESSELHOEFT

FRANKLIN W. WHITE

### COMMITTEE ON HALL

FRANKLIN W. WHITE

### COMMITTEE ON CLINICS

HENRY A. CHRISTIAN

CHESTER M. JONES

ELLIOTT P. JOSLIN

GEORGE R. MINOT

JOSEPH H. PRATT

CONRAD WESSELHOEFT

### COMMITTEE ON ENTERTAINMENT

RANDALL CLIFFORD

WILLIAM B. BREED

FRITZ B. TALBOT

### PRELIMINARY PROGRAM

### ANNUAL CLINICAL SESSION

### THE AMERICAN COLLEGE OF PHYSICIANS

APRIL 8-12, 1929

Monday, April 8, 1929

OPENING SESSION, 2 30 O'CLOCK

Hotel Statler Ballroom

1 Addresses of Welcome David L. Edsall, Dean of Harvard Medical School  
Alexander S. Begg, Dean of Boston University Medical School  
A. Warren Stearns, Dean of Tufts College Medical School

John M. Birnie, President of Massachusetts Medical Society  
Lincoln Davis, President of Suffolk District Medical Society

2 Reply to Addresses of Welcome  
Charles F. Martin, President of The American College of Physicians

3 Tuberculosis A Confession of Faith  
Lawrason Brown, Saranac Lake, N. Y.



4 (Title not yet announced) Lewellys F Barker, Baltimore

5 Juvenile Diabetes I M Rabinowitch, Montreal

6 Glycosuria James E Paullin, Atlanta

7 Clinical Aspects of Paroxysmal Hypertension M C Pincoffs, Baltimore

EVENING SESSION, 8 00 O'CLOCK  
Hotel Statler Ballroom

*Symposium on Deficiency Diseases*

1 The Fundamental Nature of Deficiencies George R Minot, Boston

2 Pathology of Deficiencies S Burt Wolbach, Boston

3 Biochemistry and Physiology of Deficiencies George R Cowgill, New Haven

4 Pernicious Anemia Randolph West, New York

Tuesday, April 9, 1929

MORNING, 9 00 TO 12 00 O'CLOCK  
Hospital Clinics

AFTERNOON, 2 30 TO 5 00 O'CLOCK  
Hotel Statler Ballroom

1 Fatigue and Infection W L Holman, Toronto

2 Neoplasms J B Murphy, New York

3 Specific Dynamic Action of Protein, Fat and Carbohydrate in Altered States of Nutrition Edward H Mason, Montreal

4 The Relation of Neisserian Infection to the Various Types of Arthritis O H Perry Pepper, Philadelphia

5 The Fallacy of Vaccine Therapy Charles C Bass, New Orleans

6 The Treatment of Angina Pectoris Harlow Brooks, New York

7 The Coronary Problem Arthur R. Elliott, Chicago

8 Clinical Aspects of Trichuriasis Lewis A Conner, New York

9 An Intensive Clinical Study of a Graphic Method of Recording Blood Pressure Louis F Bishop and Louis F Bishop Jr., New York

EVENING SESSION, 8 00 O'CLOCK  
Hotel Statler Ballroom

1 Psychiatry in Relation to Medicine Austin F Riggs, Stockbridge, Mass

2 Syphilis of the Adrenals and Its Relationship to the So-called Idiopathic Addison's Disease Aldred S Warthin, Ann Arbor

3 Lung Syphilis R I Rizer, Minneapolis

A smoker will follow this session

Wednesday, April 10, 1929

MORNING, 9 00 TO 12 00 O'CLOCK  
Hospital Clinics

AFTERNOON, 2 30 O'CLOCK  
Hotel Statler Ballroom

1 The Treatment of General Paresis Harry C Solomon, Boston

2 Psychiatry's Part in Preventive Medicine Arthur H Ruggles, Providence

3 The Need of Emotional Data in the Medical History John Favill, Chicago

4 Milder Forms of Coronary Obstruction James B Herrick, Chicago

5 The Failing Heart of Middle Life David Riesman, Philadelphia

6 Hypertension George C Hale, London, Ont

7 Undulant Fever in the United States George Blumer, New Haven

8 (Title not yet announced) Robert A Cooke, New York

9 Tobacco Smoking and Gastric Symptoms Irving Gray, Brooklyn

EVENING SESSION, 8 00 O'CLOCK  
Hotel Statler Ballroom

1 Serums and Vaccines in the Prevention and Treatment of Disease Benjamin White, Boston

2 Clinico-Roentgenological Conference M C Sosman and Associates, Boston

Thursday, April 11, 1929

MORNING, 9 00 TO 12 00 O'CLOCK  
Hospital Clinics

AFTERNOON, 2 30 O'CLOCK  
Hotel Statler Ballroom

1 The Treatment of Acute Asphyxia Cecil K Drinker, Boston

2 The Significance of Abnormal Metabolic Features in the Management of Thyrotoxicosis Walter W Palmer, New York

3 Can or Will the Internist Practice Preventive Medicine? George H Bigelow, Boston

4 Factors in the Prognosis of High Blood Pressure W W Herrick, New York

5 The Carotid Sinus Reflex (Hering), Its Use in the Diagnosis and Treatment of Certain Cardiovascular Diseases C Saul Danzer, Brooklyn

6 Lead Poisoning from Snuff Raymond J Reitzel, Galveston

The General Business Meeting of The College will be held at 4 00 in the Hotel Statler Ballroom All Masters and Fellows should attend

#### EVENING, 7 00 O'CLOCK

Annual Banquet of The College

To be followed by a Dance

Address George E Vincent, President of Rockefeller Foundation

Friday, April 12, 1929

MORNING, 9 00 TO 12 00 O'CLOCK

Hospital Clinics

AFTERNOON, 2 30 O'CLOCK

Hotel Statler Ballroom

1 Motion Picture Demonstrating Its Value in Teaching Electrocardiographic Interpretations of Cardiac Arrhythmias Joseph B Wolffe, Philadelphia

2 Dr William Dunlop and Pioneer Canadian Medicine J W Crane, London, Ont

3 Rheumatic Fever Homer F Swift, New York

4 (Title not yet announced) J C Meakins, Montreal

5 Results to Be Expected in Malignant Disease Treated by Radiotherapy George E Pfahler, Philadelphia

6 The Problem of the Nervous Patient Charles H Nielson, St Louis

7 Endogenous Obesity—A Misconception L H Newburgh and M W Johnston, Ann Arbor

#### EVENING SESSION, 8 00 O'CLOCK

Hotel Statler Ballroom

Convocation Exercises

The General Profession is cordially invited No special admission tickets are required

1 Convocation Ceremony.

2 President's Address Charles F Martin, Montreal

### PRELIMINARY PROGRAM OF SPECIAL CLINICS AND DEMONSTRATIONS

This year the general session will be held in the afternoons and evenings, while clinics and demonstrations will be held in the mornings from 9 00 to 12 00

Special Admission Cards required Clinic reservation forms and full directions will accompany the Final Program Reservations may be made by mail or daily at the Registration Bureau

Special clinics and demonstrations will be held as follows

#### A BETH ISRAEL HOSPITAL

Program in charge of Herrman L Blumgart

B

## BOSTON CITY HOSPITAL

1 (A guest will give a clinic at this time, the name will be announced later)

2 The Progress of the Boston City Hospital John J Dowling, Superintendent

3 Treatment of Pneumonia Demonstration of Cases Edwin A Locke

4 Clinic of Unusual Cases Francis W Palfrey

5 Pernicious Anemia Demonstration of Cases William B Castle

6 Treatment of Anemias Demonstration of Cases George R Minot

WEDNESDAY, APRIL 10, 1929

1 (A guest will give a clinic at this time, the name will be announced later)

2 Gastro-Intestinal Cases Franklin W White

3 Cardiac Cases William H Robey

4 Nephritis Cases William R Ohler

5 The Surgical Treatment of Pulmonary Tuberculosis Demonstration of Cases Edward D Churchill

Hypertension and Arteriosclerosis Demonstration of Cases Soma Weiss

THURSDAY, APRIL 11, 1929

1 Cardiac Cases Edward N Libby and Thomas J O'Brien

2 A Case Illustrating the Value of the Electrocardiogram James M Faulkner

3 Epilepsy William G Lennox

4 Diseases of the Coronary Vessels Demonstration of Cases Joseph T Wearn

5 Peptic Ulcer Demonstration of Cases Maurice Fremont-Smith

6 Neurological Cases Stanley Cobb

7 (A guest will give a clinic at this time, the name will be announced later)

FRIDAY, APRIL 12, 1929

1 (A guest will give a clinic at this time, the name will be announced later)

2 Cases of Disease of the Hemopoietic System Ralph C Larrabee

3 Lymphoblastoma Demonstration of Cases Henry Jackson, Jr

4 Tropical Diseases Demonstration of Cases George C Shattuck

5 Fluoroscopic Diagnosis in Chest Conditions Demonstration of Cases Harold W Dana

6 Carcinoma of the Head or the Pancreas Demonstration of Cases Irving J Walker

C

BOSTON CITY HOSPITAL  
THORNDIKE MEMORIAL LABORATORY

WEDNESDAY AND THURSDAY

APRIL 10 AND 11

BETWEEN 10 30 AND 12 30

Demonstration of Researches Concerning the Following Topics

Dr Castle and Associates

Dr Jackson and Associates

Dr Lawrence and Associates

Dr Lennox

Dr Minot and Associates

Dr Nye and Associates

Dr Wearn and Associates

Dr Weiss and Associates

Anemia

Malignant Tumors

The Physiology and Pathology of White Cells

Epilepsy

The Blood

Bacteriological Problems

The Capillaries

Various Problems

# BOSTON CITY HOSPITAL SOUTH DEPARTMENT

Program in charge of Edwin H Place

Ward visits on (1) diphtheria, (2) scarlet fever, (3) a few of the other minor groups such as chicken pox, mumps, measles and whooping cough

Amphitheater demonstration of cases of chronic laryngeal injury and other damages resulting from contagious diseases

E

## BOSTON DISPENSARY

TUESDAY, APRIL 9, 1929

- |   |  |
|---|--|
| 1 Heart Disease David Davis                 | 4 Chronic Pancreatic Disease Bert B Hershenson |
| 2 Essential Hypertonia David Ayman          | 5 Tuberculosis H Louis Kramer                  |
| 3 Neurological Clinic A Warren Stearns      |  |
| 4 Obesity Mark Falcon-Lesses                |  |
| 5 Gastro-Intestinal Clinic Percy B Davidson |  |

THURSDAY, APRIL 11, 1929

- |   |
|---|
| 1 Neurosyphilis. Arthur Beck  |
| 2 Neurasthenia Joseph H Kaplan  |
| 3 Nephrosis Tobert W Buck   |
| 4 Domiciliary Medicine in Clinical Teaching—Selected Case Osadore Olef. |
| 5 Domiciliary Medicine in Clinical Teaching—Selected Case Charles Korb  |
| 6 Diabetes James H Townsend   |

WEDNESDAY, APRIL 10, 1929

- |                                   |
|-----------------------------------|
| 1 Bronchiectasis William Dameshek |
| 2 Psychalgia Joseph H Pratt       |
| 3 Arthritis John D Adams          |

F

## CHILDREN'S HOSPITAL

Program in charge of Kenneth D Blackfan

G

## HOMEOPATHIC HOSPITAL EVANS MEMORIAL CLINIC

TUESDAY, APRIL 9, 1929

- |   |
|---|
| 1 Sterility Clinic Special Emphasis to be Placed on the Constitutional Factors in Sterility S R Meaker and A W Rowe |
|---|

WEDNESDAY, APRIL 10, 1929

### Endocrine Clinic

- |  |
|--|
| 1 Endocrine Diagnosis and Therapy Charles H Lawrence   |
| 2 Endocrine Disorders Associated with Otosclerosis and the Meniere Syndrome D W Drury                                  |
| 3 Eye Findings in Endocrine Disorders W D Rowland  |
| 4 Cases Presenting Outward Evidence of Endocrine Disorders. Found on Study not to Have Endocrine Disturbance. A W Rowe |

- |  |
|--|
| 5 Dementia Praecox. L G Hoskins  |
| 6 The Follicular Hormone J. C Janney   |
| 7 Discussion on Sugar Metabolism as Influenced by Insulin in Pituitary Disease. H Ulrich and A W. Rowe |

THURSDAY, APRIL 11, 1929

### General Medical Clinic

- |   |
|---|
| 1 Heart Clinic W D Reid   |
| 2 Intestinal Migraine C. W McClure  |
| 3 Neurology N H. Garrick.   |
| 4 Lung Abscess, Diagnosis and Treatment. Bronchoscopy, the Use of the Bronchoscope in Diagnosis and Treatment L R Johnson |

FRIDAY, APRIL 12, 1929

(Program to be announced later)

## H MASSACHUSETTS GENERAL HOSPITAL

- 1 Clinic by James E. Paullin, Atlanta
- 2 Thoracic Clinic Frederick T. Lord
- 3 Cases of Hypertension William B. Breed
- 4 Cardiac Clinic Howard B. Sprague
- 5 Endocrine Clinic Walter Bauer and Dwight L. Sisco

WEDNESDAY, APRIL 10, 1929

- 1 Clinic by Lewellys F. Barker, Baltimore
- 2 Demonstration of Medical Cases William B. Robbins
- 3 Pediatric Clinic Fritz B. Talbot and Harold L. Higgins
- 4 Clinico-pathological conference Richard C. Cabot and Tracy B. Mallory
- 5 Diabetic Clinic Roy R. Wheeler

THURSDAY, APRIL 11, 1929

- 1 Clinic by O. H. Perry Pepper, Philadelphia
- 2 Neurological Clinic James B. Ayer
- 3 Psychotherapy of Gastro-Intestinal Diseases William Herman
- 4 Gastro-Intestinal Clinic Chester M. Jones
- 5 Indications for Splenectomy. Arlie V. Bock.
- 6 Cases of Pernicious Anemia Wyman Richardson

FRIDAY, APRIL 12, 1929

- 1 Clinic by J. C. Meakins, Montreal
- 2 Demonstration of Cases Gerald Blake
- 3 Medical Clinic James H. Means
- 4 Demonstration of Cases F. Dennette Adams
- 5 Anaphylaxis Clinic Francis M. Rackemann

## I NEW ENGLAND BAPTIST HOSPITAL

Program in charge of Albert A. Hornor

## J NEW ENGLAND DEACONESS HOSPITAL

Program in charge of Elliott P. Joslin

- |  |  |
|--|--|
| 1 Carcinoma of the Colon and Colitis from the Surgical Point of View Daniel F. Jones | 4 Pedigreed Diabetics Elliott P. Joslin    |
| 2 Gastro-Intestinal Cases Sara M. Jordan and Chester Kiefer                          | 5 Surgery in Diabetics L. S. McKittrick    |
| 3 Thyroid Cases Frank H. Lahey   | 6 The Pathology of Diabetes Shields Warren |

There will be further additions to this program including clinics by larynologists, ophthalmologists, gynecologists and roentgenologists

## K PETER BENT BRIGHAM HOSPITAL

- |   |   |
|---|---|
| 1 Diagnosis of Certain Forms of Heart Disease Lewis A. Conner, New York | 4 Some Considerations on the Relation of Cardio-Renal System to Surgery of the Urinary Organs William S. Quirby |
| 2 Chronic Myocardial Disease Henry A. Christian                         | 5 Bronchoscopy in Lung Disease Lamm C. Richards   |
| 3 Results of Treatment of Duodenal Ulcer E. S. Emery                    |   |

## WEDNESDAY, APRIL 10, 1929

1. Cardiac Disease, the Result of Infectious Processes James B Herrick, Chicago

2 Gallbladder Disease Channing Frothingham

3 Bronchial Asthma I. Chandler Walker.

4 Anemia William P Murphy

5 Thrombophlebitis John Homans

## THURSDAY, APRIL 11, 1929

1 Mitral Stenosis David Riesman, Philadelphia

2 Signs of Persisting Infection in Acute Rheumatic Fever Clifford L Derick

3 Hemorrhagic Nephritis James P O'Hare

4. A Surgeon's Views of the Treatment of Peptic Ulcer David Cheever

5 Neurosurgical Conditions Harvey Cushing

## FRIDAY, APRIL 12, 1929

1 Hypertension Charles F Martin, Montreal

2 Vascular Disease in Diabetes Mellitus Reginald Fitz

3 Treatment of Certain Types of Cardiac Arrhythmia Samuel A. Levine

4 Treatment of Trifacial Neuralgia Gilbert Horrax

5 Diuretics Henry A Christian

L

## ROBERT BRECK BRIGHAM HOSPITAL

Program in charge of Louis M Spears  
Clinics on Arthritis

M

## UNITED STATES NAVAL HOSPITAL

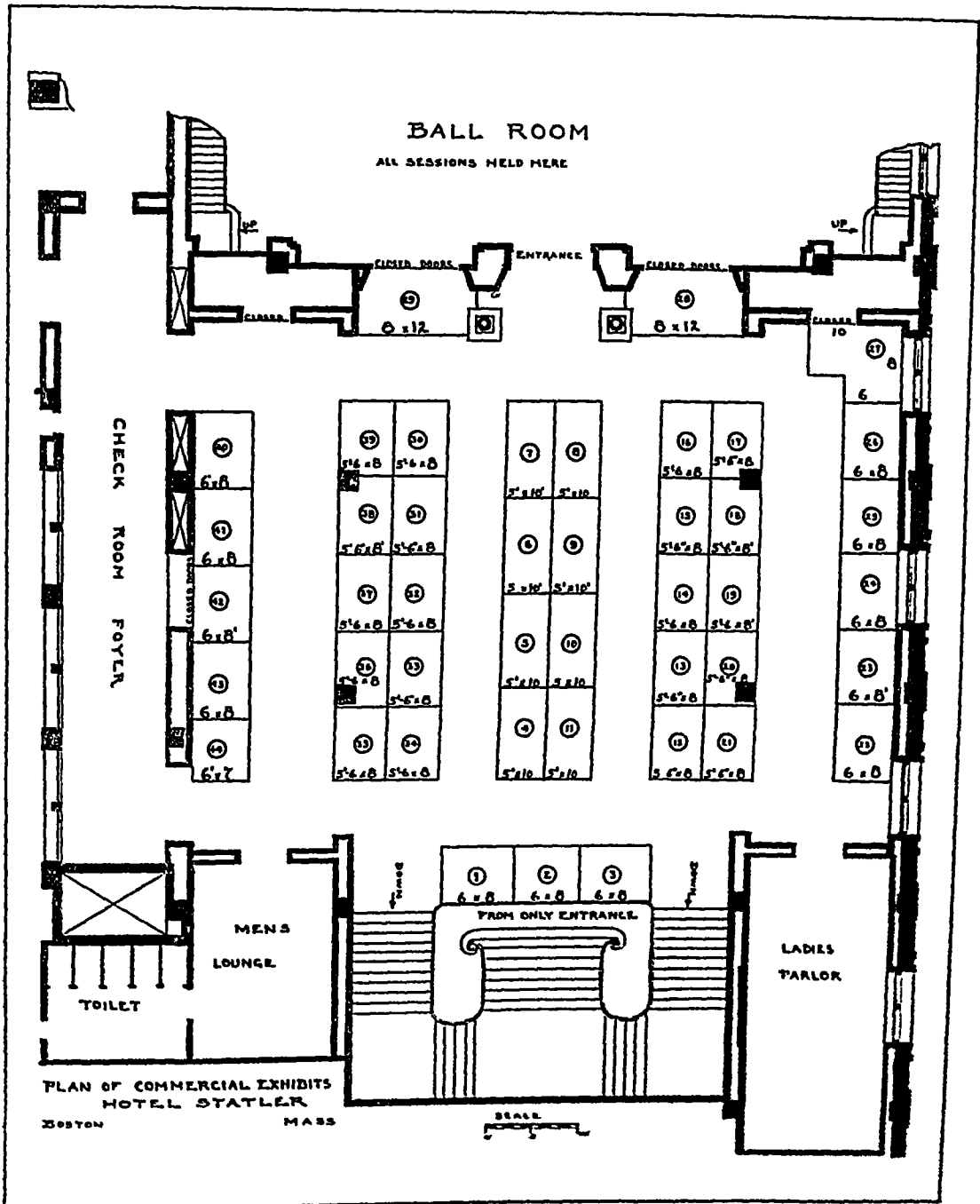
Program in charge of Capt F L Pleadwell, MC, U S N

Presentation of medical cases in the conference room of the hospital each morning. Following this the group will be split up in sections of five. Each section will be in charge of a ward medical officer, and the balance of the morning will be devoted to ward rounds.

## TECHNICAL EXHIBIT

The technical exhibits have been arranged by the Executive Secretary, Mr E R Loveland, and the following chart shows the arrangement of booths and the assignment to exhibitors from various parts of the country. The exhibits are highly diversified in their variety and will bring to the attendants at the Clinical Session, the latest and most improved equipment, the best pharmaceutical products, almost the whole library of medical publications and many other products of special interest to the Internist, Pediatrician, Neurologist, Psychiatrist, Radiologist and research worker.

This Exhibit is undoubtedly the best arranged and the most popular one that The College has yet had. The location is in the Ballroom Foyer where all attendants to the meeting will pass through the exhibits daily. The Joseph T Griffin Decorating Company, of Louisville, Kentucky, who installed the exhibits for the American Medical Association, the Southern Medical Association and many other prominent medical societies, will be in charge of the booths and decorations.



## LIST OF EXHIBITORS

SPACE	NAME	CITY AND STATE	PRODUCT
20	Abbott Laboratories	North Chicago, Ill	Pharmaceutical Products
12 & 21	D Appleton & Company	New York, N Y	Medical Publications
31	The Battle Creek Food Company	Battle Creek, Mich	Health Foods
22	Bausch & Lomb Optical Co	Rochester, N Y.	Microscopes, Photomicro & Projection Apparatus
40	P Blakiston's Son & Co	Philadelphia, Pa	Medical Publications
13	The Borden Sales Company, Inc	New York, N Y.	Merrell Soule Infant Foods
26	Britesun, Inc	Chicago, Ill	Therapeutic Lamps
25	Cambridge Instrument Co, Inc	New York, N Y	Electrocardiographs & Accessories, and other Physiological Instruments
3	Cameron's Surgical Specialty Co	Chicago, Ill	Electro-Diagnostic Surgical & Dental Instruments
44	G W Carnrick Co	Newark, N J	Pharmaceutical Products
1	Warren E Collins, Inc	Boston, Mass	Metabolism and Oxygen
49	Davies, Rose & Co, Ltd	Boston, Mass	Trethylene, Pil Digitalis, Shadocal
14	F A Davis Company	Philadelphia, Pa	Medical Publications
16	Deshell Laboratories, Inc	Chicago, Ill	"Petrolagar"
42 & 43	General X-Ray Company	Boston, Mass	"Morse" Wave Generator, GX-Galvane-Faraday Plate, Diathermy Apparatus, Electrodes
34	Paul B Hoeber, Inc	New York, N Y	Medical Publications
19	Horlick's Malted Milk Corporation	Racine, Wis	Malted Milk Products
17	Kalak Water Company, Inc	New York, N Y.	Kalak Water
4	Charles B Knox Gelatine Co, Inc.	Johnstown, N Y.	Knox Gelatine
15	Lavoris Chemical Company	Minneapolis, Minn	"Lavoris"
45	LaMotte Chemical Products Co	Baltimore, Md	LaMotte Blood Chemistry Outfits
30	Lea & Febiger	Philadelphia, Pa	Medical Publications
47	Lederle Antitoxin Laboratories	New York, N Y	Biological Products and Pharmaceutical Specialties
9	J B Lippincott Company	Philadelphia, Pa	Medical Publications



29	MacGregor Instrument Company	Needham, Mass	Vim Stainless Steel Needles, Vim Emerald Luer Syringes, Vim Surgical & Medical Specialties Medical Publications
8	The Macmillan Company	New York, N Y	Anaesthetic Apparatus, Laboratory Equipment, Diagnostic & Scientific Apparatus, Vaccines, Intravenous Products, Orthopedic Appliances & Supplies, Instruments for Operating Room, E F M Catgut
2	E F Mahady Company	Boston, Mass	Malpractice Insurance
18	The Medical Protective Company	Chicago, Ill	Melin's Food
24	Melin's Food Company	Boston, Mass	Pharmaceutical Products
38	Merck & Company, Inc	Rahway, N J	Pharmaceutical Products
23	The Wm S Merrell Company	Cincinnati, Ohio	Infant Foods
12 & 37	Merrell Soule Company	New York, N Y	Medical Publications
35	The C V Mosby Company	St Louis, Mo	Medical Publications
39	Thomas Nelson & Sons	New York, N Y	Cod Liver Oil
28	The E L Patch Company	Boston, Mass	"Helloglass"
6	Pittsburgh Plate Glass Co	Pittsburgh, Pa	Psyllium Seed & Acidophilus Products
7	Richards, Inc	Glenolden, Pa	Medical Publications
11	W B Saunders Company	Philadelphia, Pa	"Graphic" Metabolism Apparatus
27	Sinborn Company	Cambridge, Mass	Optical Instruments, Projection Apparatus, Laboratory Equipment
11	Spencer Lens Company	Boston, Mass	Pollens, Ephedrine Preparations, Dextrose Ampoules and other Pharmaceutical Products
21	Savin-Myers Co	Indianapolis, Ind	Cod Liver Oil
16	Talbly-Nelson Company	Boston, Mass	"Tyco's" Sphygmomanometer, Thermometers and Hygrometers
51	Taylor Instrument Companies	Rochester, N Y	Electrocardiograph & Quartz Lamps
5 & 10	Victor X-Ray Corporation	Chicago, Ill	Vita Glass
"	Vitronics Corporation	New York, N Y	Pharmaceutical Products
33	Winthrop Chemical Company, Inc	New York, N Y	
	{ H A Metz Laboratories, Inc		

## BAUSCH &amp; LOMB CO

Booth 22

In each issue of this publication for the past few months, this space has been devoted to a brief description of a partial list of the optical instruments which Bausch & Lomb manufacture for the medical Profession

At the American College of Physicians meeting, April 8-12, 1929, the instruments which have been described herein will be on exhibit. A list of the instruments to be exhibited are

Microscopes

Microtomes

Colorimeters

Hemoglobinometers

Centrifuges

Haemacytometers

The physician who is contemplating buying new instruments will find this exhibition an excellent place to make his choice. Undoubtedly some who do not intend to purchase will be able to obtain a great deal of useful information on new instruments and improved methods, which should aid them in their practice.

Literature which will give a comprehensive knowledge of the latest developments in the field can be had at the Bausch & Lomb booth. If, however, you do not attend the meeting, the literature will be sent to you upon application to the Company.

## P BLAKISTON'S SON &amp; CO

Booth 40

The translation of Kaufmann's Pathology by Dr Stanley P Reimann, published by Blakiston in January, makes available to all American physicians and scientists a work of international repute, whose usefulness has been confined previously to those having a high aptitude for scientific German. The work is a most complete human pathology, general and special. Subjects of most importance to the practicing physician are emphasized and given in great detail. The work is in three volumes and contains 1072 illustrations, those of the last German edition being amplified by many unique pictures drawn by the staff artist at the Lankenau Hospital. A descriptive prospectus will be sent by the publisher upon request.

## THE BORDEN SALES COMPANY, INC

Booth 13

In 1856 the first successful process for condensing milk was patented by Gail Borden. Today, 73 years later, the annual world production of all forms of concentrated milk amounts to more than three billion pounds, of which approximately 60 per cent is manufactured in the United States. The Borden Company continues to be the leading producer and distributor of condensed, evaporated, powdered and malted milks, and other milk products.

## DESHELL LABORATORIES, INC

Booth 16

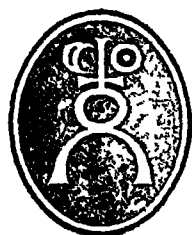
Prominent among the exhibits at the next Clinical Session will be Petrolol<sup>TM</sup>—an emulsion of mineral oil.

Samples and literature pertaining to the wide application and usefulness of Petrolol<sup>TM</sup> may be obtained by addressing 536 Lake Shore Drive, Chicago, Illinois.

## THE WM S MERRELL COMPANY

Booth 23

This is the new symbol of the Wm S Merrell Company as they have begun their second century in the preparation of medicines for the use of the medical profession. This symbol is the sign used by the ancient alchemists to represent that by which perfection may be attained, the accomplishment of the ideal, the reward to those who faithfully follow the laws of their Philosophy.



The Merrell Symbol was also used by the Alchemists to represent the Elixir of Life, which, if taken according to instructions, would heal the sick and renew the life of the old. Needless to say, such an Elixir remained as an ideal and was never found. The development of rational Therapeutic agents in the closest approximation of the ideal that has as yet been made.

## SANBORN COMPANY

— 27 —

METABOLISM testing with simplified apparatus giving reliable data for diagnosis will be demonstrated at Space 27 by Sanborn Company. This Company manufactures and supplies directly to physicians and hospitals. Medical conventions afford special opportunity for Sanborn owners and prospective owners to get practical information of the latest and best methods of testing. The new and approved Sanborn ELECTROCARDIOGRAPH—portable and transportable models—the least expensive but the best, will gladly be explained. Visit Space 27.

## TAYLOR INSTRUMENT COMPANY

— 51 —

One of the exhibits by the Taylor Instrument Companies will be the Tycos Sphygmomanometer.

The Tycos Recording Sphygmomanometer introduces a means of measuring blood pressure which necessitates neither stethoscope nor indicator, its automatic nature insuring an exactness of systolic and diastolic pressure points never before attained.

In addition, any cardiac irregularity producing characteristic changes in the brachial artery is identified by the Tycos tracing.

This is best realized by an inspection of the actual graphs of various pathologies which are included in their latest booklet, 'The Clinical Use of the Tycos Recording Sphygmomanometer.' Copy will be sent upon request.

Dr F M Pottenger (Fellow and Regent) Monrovia, California, and Dr Egerton Crispin (Fellow and Governor), Los Angeles, California, sponsored a subscription dinner of the Fellows and Associates of The College at the California Club, Los Angeles, on January 18.

The purposes, ideals and future plans of The College were presented, and Dr Leonard G Rountree (Fellow), Professor of Medicine at the University of Minnesota and Director of the Medical Service at the Mayo Clinic, delivered an address on 'Recent Advances in the Knowledge of the

Liver. Such gatherings of members of The College are inspiring and helpful and it is hoped that groups in other parts of the country will follow this plan of coming together socially and professionally.

Dr C W Stone (Fellow) Cleveland is President of the Ohio State Medical Association and will preside at the convention to be held in Cleveland in May.

Dr Howard T Kerner (Fellow), Cleveland has resumed his duties at the Western Reserve University.

leave of absence with the National Research Council at Washington

The summer of 1929 will see the new Institute of Pathology at the University opened. Dr Karsner will head this Institute

Dr Clyde L. Cummer (Fellow), Cleveland, is Councilor for the Fifth District of the Ohio State Medical Association. This year the State Association holds its Convention at Cleveland

Dr Morris Weissberg (Fellow), Brooklyn, read a paper entitled "Xanthoma Diabeticorum" on December 12, 1928 before the Brooklyn Medical Association

Dr John J. Pfluck (Associate), Chicago, has been appointed by Dr Kegel, Health Commissioner of Chicago, as a member of the Advisory Council Staff of the Chicago Health Department

At a recent meeting of the Advisory Committee, Dr Alvah A. Swayze's resignation as head of the Medical Division of the Hackensack Hospital was accepted with regrets. Dr Heiman Trossbach of Bogota was appointed to fill the vacancy

Dr Elliott B. Edie (Fellow), Uniontown, Pa., was elected Chairman of the Medical Section of the Pennsylvania State Medical Society at its last meeting. The Section officers are responsible for the preparation of the program for the annual meeting, which will be held in Erie, September 30, 1929

Dr Edie is in charge of a Heart Clinic, which opened in Uniontown, January 8, 1929, at the suggestion of the Pennsylvania Heart Association. The Pennsylvania State Department of Health will furnish the supplies and nursing service. The Clinic will be open every Tuesday at 11 o'clock in the Red Cross Rooms, Fayette Title & Trust Building

Dr John F. Kenney (Associate), Pawtucket, R. I., at the request of the Rhode Island State Welfare Commission recently

completed a reorganization of the Laboratory of the State Hospital

Drs F. C. Oldenburg (Fellow) and H. V. Paryzek (Fellow), both of Cleveland, were elected to the Board of Directors of the Academy of Medicine of Cleveland at its recent annual meeting. They will serve for a period of three years

Dr Oldenburg has been promoted to Senior Clinical Instructor in Medicine at the Western Reserve University Medical School, he is also Secretary and Treasurer of the Western Reserve Medical Alumni Association, and Secretary of the Staff of St. Vincent de Paul Charity Hospital in Cleveland

Dr G. T. Harding, Jr (Fellow), Columbus, Ohio, is President of the Columbus Academy of Medicine for the year 1929

Dr J. W. Torbett (Fellow), Marlin, Texas, reports that the Torbett Sanatorium has taken over the Imperial Hotel owned by Dr J. W. Cook, recently deceased, and combined the institutions all in one known as the "Torbett Sanatorium, Majestic Hotel and Annex." The new institution has 175 beds with all departments in proximity to one another for diagnosis and treatment of all classes of chronic diseases and especially catering to the tourists of the North who come to Texas for the winter. The dining room is under the supervision of an expert dietitian, and ten doctors comprise the staff

Dr L. D. Sargent (Fellow), Washington, Pa., has recently returned from a European trip of three months. His time in London and Paris was devoted entirely to the study of diseases of the heart and lungs

Dr Robert M. Moore (Fellow), Indianapolis, on January 10 addressed the McLean County Medical Society at Bloomington, Illinois, his subject being "Some Considerations in Heart Failure of the Anginal Type"

Dr Ray M Balyeat (Fellow), Oklahoma City, read a paper on "Perennial Hay-Fever" at the Asheville Meeting of the Southern Medical Association, and the discussion was opened by Dr Grafton Tyler Brown (Fellow), Washington, D C

Dr Howard L Hull (Fellow), Elma, Washington, was elected President of the Grays Harbor County Medical Society for 1929

Dr William J Mallory (Fellow), Washington, D C, read a paper on "Diet in Diabetes" before the American Dietetic Association at its meeting in Washington, October 29-31, 1928

By invitation, he also read a paper before the annual meeting of the Seaboard Medical Association of Virginia and North Carolina, December 4-6, 1928, Washington N C, on "The Management of the Complications of Diabetes, Acidosis and Infection" "Gas on the Stomach, a disturbance of Motor Function" was the title of another paper, which Dr Mallory read before the George Washington University Medical Society, recently

Dr Wilfred E Chambers (Fellow), Medical Officer in Charge, U S Veterans Hospital, Kansas City, Missouri, addressed the War Mothers of Missouri and Kansas at Memorial Hall, Independence, Mo, October 16, 1928 on the medical care and treatment of the ex-service disabled of the U S Military forces

He also addressed the Gold Star Mothers of Missouri at the Hotel Muelbach, Kansas City, November 13, 1928, on the medical care and treatment of the ex-service of the U S Military Forces in foreign countries and disabled ex-service of our Allies in the United States

On September 20, 1928 Dr Chambers addressed the Veterans of Foreign Wars at Kansas City on hospitalized patients who had previously fallen into the hands of

the charlatan and the evil results thereof, financially, mentally and physically

An article entitled, "Rehospitalization" by Dr Chambers, published in the January 1929 issue of the U S Veterans Bureau Bulletin, will be of interest to those concerned directly, or indirectly, with the medical care and treatment of ex-service men of the U S Military Forces

Dr I D Bronfin (Fellow), addressed the Colorado Tuberculosis Association on January the twenty-fifth, 1929, on "Tuberculous Infection and Disease in Childhood" and the Public Health Section of the Colorado State Nurses Association on February the seventh, 1929, on the subject of "Juvenile Tuberculosis"

Dr Louis O S Wallace (Fellow) formerly of Kalamazoo, Michigan, was recently appointed First Assistant Physician on the Medical Staff of the Sonoma State Home at Eldridge, California

Dr Wallace has been elected to membership in the American Psycho-Pathological Association and in the American Association for the Advancement of Science

Dr Albert B Yudelsohn (Associate), Assistant Professor of Neurology, Northwestern University Medical School, Chicago read a paper entitled "Remission of Tabetic Symptoms Following Sacral Injection of Physiological Solution" on December 20, 1928, before the Chicago Neurological Society Dr Yudelsohn has spent fifteen months investigative work on this subject and uses lantern slides and demonstrates the technique when presenting the paper

In the Editorial on the Early Manifestation of Leprosy in the November issue of the Annals the Director of the Leprosy Receiving Station in Honolulu should have been given as N E Watson and not J T Watson who was the former Director of the Station

## OBITUARY

Dr Eugene Wilson Murray (Fellow, February 8, 1921), Newark, New Jersey, died September 18, 1928, aged 54 years

Dr Murray, after graduating from the Northwestern University, School of Pharmacy, attended the Syracuse University, College of Medicine, receiving his medical degree in 1898. He was an interne at the New York City Hospital 1898-99, Attending Physician to the Presbyterian Hospital (Newark) 1913 —, Medical Director of the Newark Babies' Hospital 1916 —. He was a member of the Phi Kappa, Psi Upsilon and the Nu Sigma Nu Fraternities, also a member of his County and State Medical Societies and the American Medical Association

Dr John Lincoln Macumber (Fellow, December 27, 1919), Brooklyn, N Y, died December 22, 1928, of cerebral hemorrhage, aged 67 years

Dr Macumber graduated from the Long Island College Hospital, Brooklyn, in 1883, and pursued postgraduate study later at Columbia University College of Physicians and Surgeons and at Fordham University School of Medicine. From 1886 to 1889, he was assistant physician to the Kings County Insane Asylum and superintendent of the same institution from 1890 to 1891. His more recent appointments were: consulting neurologist, Brooklyn States Hospital, 1900 —, clinical assistant neurologist, Van derbilt Clinic, 1908 —, attending psychiatrist, Kings County Hospital, 1925

—, clinical instructor, Long Island College Hospital, 1926 —, attending neurologist, Swedish Hospital, 1902 —, attending neurologist, St Catherine's Hospital, 1913 —, attending neurologist, Lutheran Hospital, 1921 —

In addition to being a Fellow of the American College of Physicians, Dr Macumber was a member of his County and State Medical Societies, and a Fellow of the American Medical Association

Dr Marinus Laisen Holm (Fellow), Lansing, Mich, died December 24, 1928, of pulmonary tuberculosis, aged 50

Dr Holm was born in Denmark in 1878, and came to the United States at an early age. He received his Ph G and Ph C degrees from the Northwestern University School of Pharmacy, and then completed the medical course in the medical department of the same institution in 1907. He did postgraduate work at Paris and Dijon. From 1902 to 1903 he was instructor in pharmacy at Northwestern University, and assistant in the department of physiological chemistry in the same institution from 1903 to 1906. From 1906 to 1907, he was assistant city chemist, Chicago Department of Health, and from 1907 to 1916, state bacteriologist for the state of Michigan, from 1910 to 1921 he was pathologist of the Sparrow Hospital at Lansing, from 1912 to the time of his death he was a member of the Medical Milk Commission at Lansing, and from 1921 a member

of the Lansing Board of Health. He served during the World War with the successive commissions of Lieutenant, Captain and Major in the Medical Corps of the U S Army, and was pathologist with the American Expeditionary Forces.

Dr Holm was an ex-president of the Ingham County Medical Society, a member of the Michigan State Medical Society and a Fellow of the American Medical Association. He had been a Fellow of the American College of Physicians since 1920.

Dr Joseph Goldberger (Fellow March 10, 1923), surgeon, U S Public Health Service, Washington, D C, died January 17, 1929, due to hypernephroma of the left kidney with metastasis in the lung, aged 48 years.

Dr Goldberger received his medical degree from the Bellevue Hospital Medical College, New York, in 1895, "was commissioned in the public health service in 1899, in which his early assignments were at Tampico, Mexico, in connection with yellow fever, where he contracted the disease. He served also at Ponce, P R, Vera Cruz, Mexico, in Texas, and during the epidemic of yellow fever in the South in 1905. With the exception of absences due to such investigations as that of dengue fever in the South in 1907, at which time he contracted dengue, and the investigation of straw-rite disease in New Jersey, the cause of which he discovered, he had been

attached to the Hygienic Laboratory for many years. Other notable investigations were carried on in connection with measles and typhus fever, which he contracted in Mexico City, 1909-10. There he demonstrated that typhus can be transmitted not only by the body louse but by the head louse.

Dr Goldberger's most important research was on pellagra, beginning in 1913, he was the foremost exponent of the theory that pellagra is a nutritional disease due to unbalanced diet. In this work he performed outstanding research on animals and man, making repeated trips to the South and other parts of the country where pellagra was prevalent. Pellagra had been recognized a hundred years in the Old World but was first recognized in the United States in 1907."

Dr Goldberger was the author of a great many articles in various medical journals of the country, and had he lived would have delivered an address before the Thirteenth Annual Clinical Session of the American College of Physicians at Boston April 8-12. He was a member of the District of Columbia Medical Society, the American Medical Association, the American Association for Advancement of Science, the American Association of Pathologists and Bacteriologists and the American Public Health Association, in addition to being a Fellow of the American College of Physicians.

# Thirteenth Annual Clinical Session

of the

## AMERICAN COLLEGE OF PHYSICIANS

BOSTON, MASS., APRIL 8-12, 1929



The 1929 Clinical Session will constitute one of the most important post-graduate weeks in the history of the College. The Harvard Medical School, the Boston University School of Medicine, Tufts Medical School, Boston City Hospital, Boston Dispensary, Children's Hospital, Homeopathic Hospital, Massachusetts General Hospital, Peter Bent Brigham Hospital, Robert Breck Brigham Hospital, Beth Israel Hospital, New England Baptist Hospital, New England Deaconess Hospital, U. S. Naval Hospital, Carney Hospital and the House of the Good Samaritan are cooperating and arranging programs. Eminent authorities from all parts of the country will participate in clinics, laboratory demonstrations, symposia and formal addresses. *See the College News Notes section for additional details of the program*

*Transportation* Over all railroads of the United States and eastern Canada on the Certificate Plan of reduced fares. Special trains from and to Chicago over the Michigan Central Railroad, special trains from and to Washington over the Pennsylvania Railroad and associated roads. Time-tables for special trains may be secured from ticket offices or passenger agents of roads mentioned, or from the Executive Secretary.

*College Smoker*, Tuesday evening, April 9, *College Banquet*, Thursday evening, April 11, *Convocation*, for the conferring of Fellowships, Friday evening, April 12.

*Headquarters* Hotel Statler Make reservations immediately.

*For Information, address the Executive Secretary.*

CHARLES F. MARTIN, M.D., *President*  
Montreal, P. Q., Canada

JAMES H. MEANS, M.D., *Chairman*  
Boston, Mass.

E. R. LOVELAND, *Executive Secretary*  
133-135 South 36th Street, Philadelphia, Pa

*Please mention this Journal when writing to Advertisers*



# Insulin and Carbohydrate Tolerance\*

By ELLIOTT P JOSLIN, M D, *Boston*

**I**N the same serious spirit with which Brace<sup>1</sup> approached the problem of the effect of insulin upon the carbohydrate tolerance of diabetics, I have searched my own records and have reached a contrary and more optimistic conclusion and, I trust, explained his less favorable results. If he should reduce the total caloric intake of his patients to levels such as are accepted as normal for healthy individuals, thus involving a reduction of fat in the diet he prescribed, I believe he would be able to increase the carbohydrate in the course of a year with negligible or little increase in insulin, and thus demonstrate a gain in carbohydrate tolerance of diabetics under insulin medication.

As Brace has done and as I am now doing, it would be helpful to an understanding of the present status of diabetic treatment if other clinicians, interested in diabetes, would also publish comparable series of five diabetics who have exceptional records over an interval of at least four years.

"A failure to obtain evidence of improvement in the tolerance for glucose in five patients, who had received weighed, high fat, low protein and low carbohydrate diets and daily insulin over periods varying from 32 to 45 months, has given us no ground for believing that insulin is capable

of effecting a cure or a partial cure of human diabetes mellitus \* \* \* Each of these patients has lost tolerance during the period of treatment with insulin."<sup>2</sup>

Frankly I cannot agree with the above quotation from the conclusions of Brace's article. The protocols of his patients show that they were not receiving "low protein and low carbohydrate diets" in the Newburg and Marsh<sup>2</sup> sense (See Table 1) and the caloric values of the diet were excessive by any standard. Furthermore, support for my disagreement is afforded by the remarkably favorable course for two years of his Case V while on a constant diet of carbohydrate 64 grams, protein 66 grams, and fat 255 grams, because during this interval his daily insulin was re-

TABLE 1—THE ORIGINAL NEWBURGH MARSH DIETS

Diets	C Grams	P Grams	F Grams	Calories
1	15	20	85	914
2	20	28	120	1353
3	29	34	163	1719
4	37	54	210	2254

\*From the New England Deaconess Hospital, Boston.

<sup>1</sup>BRACE, *Annals of Internal Medicine*, 1927, 1, 203.

<sup>2</sup>NEWBURGH AND MARSH, *Arch. Int. Med.* 1920, 25, 647, also *ibid.* 1921, 27, 455.

TABLE 2—A REDUCTION OF 16 UNITS OF INSULIN IN 2 YEARS DURING TREATMENT OF A DIABETIC UPON A CONSTANT DIET

Case V, F J, Cited from Brace<sup>1</sup> Italics inserted by Author

Date	Diet			Total Glucose Gms	Insulin Units	Urine Glucose
	P Gms	F Gms	C Gms			
July 1919	53	210	37	90	0	Neg
Mar 1923	53	210	37	90	0	Neg
Mar 1923	70	290	75	144.6	26(13-13)	Neg.
Apr 1924	70	290	75	144.6	46(16-15-15)	Neg.
Aug 1924	70	290	75	144.6	41(21-10-10)	Neg
Dec. 1924	70	290	75	144.6	40(20-8-12)	Neg.
Jan 1925	66	255	64	127.7	42(20-9-13)	Neg
June 1925	66	255	64	127.7	34(13-8-13)	Neg
Aug 1925	66	255	64	127.7	27(13-5-9)	Neg
Jan 1927	66	255	64	127.7	26(12-5-9)	Neg

duced from 42 units to 26 units! See Table 2

I am not at all surprised that this same patient, Case V, irrespective of infections, increased his insulin in an earlier period between March 1923 and January 1925. At the former date upon recovery from an infection and a semi-comatose state this man, 30 years old, weight 45 kilograms, was given 50(1) calories per kilogram body weight (C 37, P. 53, F 210, Cal 2250) and before the end of the same month 71(1) calories per kilogram (C. 75, P. 70, F. 290, Cal 3190) and this diet was maintained until January 1925. Thereupon carbohydrate, protein and fat were all reduced and the striking gain in tolerance ensued. In about four years the weight rose from 45 kilograms to 55 kilograms or 21 per cent.

At no time was this patient or in fact any of the five cases cited by Brace on a low protein diet unless in the brief unpublished test periods. See Table 2. For their final diets the protein was approximately 1 gram

per kilogram body weight. The caloric values of the diets were also high and, as last recorded, were 42.9, 45.6, 40.5, 39.1, and 51.5 calories respectively per kilogram body weight. The success of the original Newburg-Marsh diets, which are shown in Table 1, can be ascribed largely to their low caloric values, quite as much as to their low carbohydrate and low protein values, but in the diets of the patients reported by Brace low protein, and indeed low carbohydrate in four of the five cases, have been discarded and the total calories have been raised considerably above the needs of healthy adults. Diabetes comes on with overfeeding rather than with underfeeding and it is against a fundamental law of diabetes to expect gains in tolerance when a patient is overfed. Under these circumstances I consider it remarkable that the patients of Brace made so good a showing, and instructive that Case V should have improved so much as to have been able to reduce his insulin 16 units a day in the course of 2 years.

TABLE 3—LAST RECORDED DIETS OF THE DIABETIC SERIES OF BRACE

Case No	Age Years	Weight Kilog	Diet in Grams			Calories		Total Glucose	Insulin Carb per unit	Total Glucose per unit	Cal per kilogram per unit
			C	P	F	per Kilog	Total Units				
									Gms	Gms	
I	LC	21	54.5	35	55	220	88.9	42.9	56	0.6	0.8
II	RB	32	60.0	60	60	280	122.8	45.6	85	1.4	0.5
III	RK	20	61.0	45	55	230	99.9	40.5	30	3.3	1.4
IV	DAH	28	63.0	60	60	220	116.8	39.1	52	2.3	0.8
V	FJ	34	54.5	64	66	255	127.7	51.5	26	4.9	2.0

The unit values for insulin in terms of carbohydrate, total glucose, and calories per kilogram are shown for Brace's cases in Table 3. Save for Case V these values seem strikingly low. In only one case was the unit value for carbohydrate above 15 grams, and in but 2 instances did the total glucose value exceed 23 grams. Two patients obtained but 0.6 and 0.7 gram carbohydrate per unit of insulin and 1.6 and 1.4 grams total glucose per unit. Despite the high caloric diets which these patients received the calories per kilogram body weight per unit insulin were meagre, amounting to 0.8, 0.5, 1.4, 0.8, and 2.0 calories respectively.

These five patients of Brace certainly obtained small returns upon their investments in insulin and this leads me now to present the other side of the question.

It is difficult for me even in the abstract to accept continued loss of tolerance or failure to gain tolerance for carbohydrate in diabetes because of the following considerations:

(1) If diabetics grow worse with time, what is the explanation for the absence of "complete" diabetes, which would seem to be the goal that all

diabetics must reach, with that premise, among my 161 patients of 20 or more years' duration? If diabetics "distinguished \*\*\* for their loyalty, honesty, intelligence" (Brace) lose tolerance, what must be the fate of the ordinary diabetic? At what rate is tolerance lost by the exemplary diabetic and by how much must one expect the rate to be accelerated in the careless?

Even careless diabetics sometimes do extraordinarily well, although I hardly dare acknowledge it. These patients in general are not susceptible to careful investigation and the only proof of the proposition is in length of life, appearance, and activity. I will mention 4 such patients by their Case numbers, 428, 1254, 1609, 1895, all of whom are described elsewhere.<sup>3</sup> The diabetes of Case No 1609 began in 1917 when he was 107 years old. It was severe in type, his weight fell from 90 to 71½ pounds during the first two years. He broke his diet continuously and it seemed a miracle that he escaped death from coma. Even with insulin he was seldom

<sup>3</sup>JOSLIN: Treatment of Diabetes Mellitus, 4th edition, Lea & Febiger, Philadelphia, 1928. Consult Case Index.

sugar-free, but 10 years later in February 1927, he appeared in my office as an attractive, healthy looking young man of twenty years, 5 feet  $7\frac{3}{4}$  inches tall, and weighing 135 pounds. His urine contained no sugar, the blood sugar eight hours after a meal was 0.21 per cent, and he was taking 10 units of insulin in the morning, 10 at noon, and 16 at night. He was working hard, carrying on his own small farm and is alive January, 1929.

(2) It is my general impression after contact with diabetics for 30 years that if they follow reasonable rules of treatment the longer they live the milder their disease becomes. My cases of long duration die of the complications of diabetes rather than of coma, and the patients who develop coma always give a history of gross indiscretions. Neither Von Noorden with his 20,000 diabetics, nor I with 7,000 believe we have encountered a complete diabetic and the few cases of insulin refractory diabetes in the literature tend to confirm the truth of our opinions. I have seen one case, Case No. 6247, of hitherto unexplained refractory diabetes,<sup>4</sup> but even that case is now explained as one of hemochromatosis as the result of an autopsy.

Diabetic mortality among individuals under 20 years of age in Massachusetts has almost reached the vanishing point,<sup>5</sup> and implies that the few who die are dying needlessly, and yet this is the group of diabetics which is supposedly severe and should become complete diabetics if their tolerance were fading away.

(3) My diabetic children daily chal-

lenge pessimism by their good looks, their vigor of mind and body, and their normal sexual development. The return of menstruation in Case No. 2617 at the age of 20 years after 63 years of diabetes occurred in June 1928, 6.5 years after it last took place. This has encouraged me very much, because I think she was one of the few exceptions I had among this type of patients. If tolerance was failing, would one expect catamenia to begin? As pulmonary tuberculosis advances, does menstruation come back? The failure of diabetes to be fatal in more than six instances among 303 of my children during the 22 months ending July 1, 1928 does not speak in favor of loss of tolerance.<sup>6</sup>

(4) The above considerations are largely general in nature. Since I have claimed so often that the tolerance in diabetes can improve, it is manifestly my duty to furnish examples. Like Brace I will cite five cases. I frankly admit that I have not like Brace omitted the insulin which these patients are taking or reverted to their original test diets in order to test their tolerance and to compare it with that at the first observation, and moreover I am unwilling to do so.

Brace describes his method as follows:<sup>1</sup> "The glucose tolerance of each individual is always determined by beginning with bed rest and a daily diet consisting of protein 20 grams, fat 86 grams, and carbohydrate 15 grams, without insulin. The total glucose con-

<sup>4</sup>JOSLIN *ibid*, p. 634

<sup>5</sup>JOSLIN: *ibid*, p. 121

<sup>6</sup>JOSLIN AND WHITE *Jour. Am. Med. Assn.*, 1929, 92, 143

tent of this diet is 30 grams. After an aglycosuric period of three to four days, each foodstuff is proportionately increased so that the next diet has a total glucose content of 50 grams and consists of protein 28 grams, fat 129 grams, and carbohydrate 20 grams. Similarly, after aglycosuria periods of the same time length, the diet is raised proportionately until its total glucose content is 70 grams, consisting of protein 34 grams, fat 163 grams, carbohydrate 29 grams. The fourth level affords 90 grams of total glucose, consisting of protein 54 grams, fat 210 grams, and carbohydrate 37 grams. To the latter diet carbohydrate is added in ten gram measures every third or fourth day, until there is a glycosuria."

I realize perfectly well that some will say my standards for the determination of the present tolerance are not as scientific as the careful regime to which Brace subjected his patients. But is his test as scientific as it seems? His patients underwent comparable tests at beginning and end of the periods of observation, it is true, but note (a) the preliminary diets for the tests were undernutrition diets whereas the endogenous metabolisms of the patients at the beginning and end of the average three years' interval were dissimilar and indeed not comparable, because of differences in body weights at the two periods, which were due to deposits of fat rather than to growth, (b) upon both occasions the stimulating effect of exercise upon carbohydrate tolerance was lost, because the patients were placed in bed, and the tests were therefore artificial; (c) the sudden restric-

tion in diets which the tests involved itself tends to lower or at least conceal tolerance for carbohydrate as proved by Odin<sup>7</sup> even for normals. This also exerted more of an influence in the second testing because the return to the diet of protein 20 grams, fat 86 grams, and carbohydrate 15 grams represented a relatively greater lowering of caloric intake than at the first test when the weights of the patients and their needs were less, (d) no adequate opportunity was given the patients to disclose their capacity for a growing tolerance. To develop a tolerance for carbohydrate it is essential that slow, gradual, and very small additions to the carbohydrate intake must be undertaken rather than sudden additions even of 10 grams. If the carbohydrate in the diet is 37 grams an increase of 10 grams amounts to an addition of 27 per cent<sup>1</sup>. If my patients could gain one gram of tolerance for carbohydrate a month what an advance that would represent compared with pre-insulin days!

A comparison of the ages of onset of the diabetes, the duration of the disease, the diets, the carbohydrate, glucose and calorie-kilogram equivalent of an unit of insulin is given in Tables 2, 4, and 5 for the five cases selected by Brace and the 5 from my series.

The ages of onset of my cases average 15 years, 8 years less than the cases of Brace, and the durations of the disease in my series average 12 years in contrast to 4 years for those

<sup>7</sup>ODIN: Acta Medica Scand 1927, Supp 18, 388.

TABLE 4—COMPARISON OF THE TWO GROUPS OF DIABETICS OF BRACE AND JOSLIN

Brace	Onset		Duration of Disease to Final Observation	
	Date	Age	Date	Duration
I (L C )	1922 June	18	1926 Jan	36
II (R B )	1922 Feb	28	1926 March	41
III (R K )	1924 Jan	18	1926 March	22
IV (D A H )	1923 Aug	25	1926 April	27
V (F J )	1919 Jan	26	1927 Jan	80
Average (years)		23	Average (years) 41	

Joslin	Onset		Duration of Disease to Final Observation	
	Date	Age	Date	Duration
359	1910 Feb	33	1929 Jan	189
632	1912 Aug	30	1929 Jan	163
1616	1919 Aug	55	1929 Jan	94
2084	1919 June	32	1928 Dec	95
2560	1921 June	5	1928 Aug	72
Average (years)		15.3	Average (years) 123	

TABLE 5—LAST RECORDED DIETS OF THE DIABETIC SERIES OF JOSLIN

Case No	Age Years	Weight Kilog	Diet in Grams			Calories per Kilog	Total Glucose	Total Units	Insulin		
			C	P	F				Carb per unit	Total Glucose per unit	Cal per kilog per unit
									Gms	Gms	
359	52	56.0	236	116	95	40	313.3	15	157	209	27
632	46	59.0	166	69	119	34	218	26	64	84	13
1616	14	32.3	128	84	132	63	190	28	46	68	23
2084	13	28.4	110	85	90	56	168	27	41	63	21
2560	12	33.9	125	65	125	56	175	22	57	80	25

of Brace The youthfulness of my patients attests to some extent their severity, but to a less degree than is ordinarily supposed. It may help to explain their gain in tolerance, because a young pancreas may be more capable of regeneration than an old pancreas. Obviously the younger age of the patients accounts for the relatively high protein and caloric values per kilogram body weight. The high protein value of Case No. 359 is in fact explained by his unusual activity

in the post-office at the Christmas season.

AUTHOR'S CASES

Case No. 359 developed diabetes at the age of 33 years in February 1910 and came under my observation in August of that year, his naked weight having fallen from 71 to 59 kilograms. He gave a history of "typhoid-malaria" in the Spanish war in 1898 and of jaundice in 1904 preceding the removal of a cystic left kidney by M. H. Richardson in February, 1905. During a part of these 19 years he has been a patient of Francis W. Palfrey whose records sup-

## Insulin and Carbohydrate Tolerance

plement my own and to whom I am greatly indebted. The percentage of glycosuria about one month after onset and 8 days after the diagnosis of diabetes was 30 per cent on March 12, 1910 according to Dr Palfrey's records. The first percentage reported to the patient was 6 per cent. He worked in the Boston Post Office but was transferred to another office and moved his home near to it. Upon June 28, 1927, his wife wrote my associate Howard Root—"Dear Sir

"I have such good news today I must tell you the credit belongs to you. Mr B received his report from U S Post

Office department for year's work. cent. They never mark 100 and very 99. This includes moral of whole neatness of reports, daily financial cc and good will of the people in the and this report was made by their ington inspectors who are trained business of looking for trouble. Oh! for I love my scales. "

The husband and wife ate 2 bushels carrots and 500 pounds of squash winter of 1919, but glycosuria appeared when the squash ripened and when vegetables were used instead of fresh tables. Washed vegetables were free

TABLE 6

Case No 359		Male		Onset at 33 years in Feb 1910					
		Weight Aug 1910, 59 kg		Weight Jan 1929, 56 kg		Height 171			
Date	Urine Per Cent	Blood Sugar Per Cent	C	P	F	Total Glucose	Naked Weight Kg.		
Mar 12, 1910	30								
Aug 15, 1910	trace								
May 29, 1912	0								
May, 1915	0								
Jan 2, 1920	0					111	54.5		
Feb 8, 1923	0	0.20 3 hrs p c	22	133	104	109	52.7		
Mar 7, 1923	0		36	90	147	103			
Nov 7, 1923	0.4 <sup>1</sup>	0.25 fasting	64	42	82	91 <sup>2</sup>	44.5		
Nov 13, 1923	0	0.22 "	78	49	121	118	43.2		
Nov 29, 1923	0	0.17 "	70	49	145	113	50.0		
Dec 13, 1923	0	0.17 "	70	49	145	113			
Déc 4, 1924	0	0.13 "	78	45	168	121	52.7		
Apr 9, 1925	0	0.21 "	98	55	167	147	50.9		
June 18, 1925	0	0.09 "	88	55	167	137	51.6		
Oct 29, 1925	0	0.07 "	90	55	167	139	51.6		
June 3, 1926	0	0.20 "	94	75	178	156	50.9		
Feb 3, 1927	0	0.05 3½ hrs p b <sup>3</sup>	109	82	183	175			
Feb 24, 1927	0	0.06 5 hrs p b	109	82	173	174			
Aug 30, 1927	0	0.18	100	82	173	174			
Nov 30, 1927	0	0.06 1½ hrs p b	109	82	173	174			
Mar 7, 1928	0	0.08 1 hr p b	126	82	140	180			
May 17, 1928	0	0.08 2½ hrs p b	151	91	118	216			
June 14, 1928	0	0.24 1 hr p b	170	95	115	237			
Oct 18, 1928	0	0.05 2 hrs p b	185	91	118	250			
Jan 10, 1929	0	0.06 3 hrs p b	235	116	95	313	55.9		

<sup>1</sup>6 grams in 24 hours

<sup>2</sup>Calculated after deduction of urine sugar

<sup>3</sup>p b signifies after breakfast

ployed In November 1923 he said he had never missed a day's work on account of diabetes in the 13 years he had had it

Despite his one kidney for 24 years his blood pressure is 110/20 and the urine contains but a very slight trace of albumin and the non-protein nitrogen in the blood is normal Wassermann negative No gall stones by symptoms or roentgen ray Diabetic heredity absent

It would appear that with the help of insulin, diet, and time, his tolerance for carbohydrate had risen from 22 grams to 236 grams

My second patient, Case No 632, is the one with the best data and if one does not concede he has gained tolerance from an examination of Table 7 there is no need of reading the balance of this paper Details about his course have been published for years,<sup>8</sup> and in January 1929 he is in better condition than ever since onset He had difficulty in becoming sugar free on carbohydrate 15 grams in 1913 at the age of 31, one year after the onset of his diabetes Gradually the carbohydrate rose to 29 grams, but in 1922 it had fallen to carbohydrate 15 grams, protein 69 grams, fat 103 grams With 26 units of insulin he was sugar free on January 2, 1929, through-

out the entire day upon carbohydrate 166 grams, protein 69 grams, and fat 119 grams The calories in the diet are 34 per kilogram body weight. The carbohydrate per unit insulin is 64 grams The total glucose per unit 83 grams, and the calories per kilogram per unit are 13 In the summer of 1928 he was selected to play in an international golf match and won distinction

Wassermann negative. Diabetic heredity absent

Upon July 10-12, 1928 the fasting blood sugar was 0.14 per cent, the blood sugar at 11 A.M. 0.08 per cent and at one hour after lunch 0.16 per cent, the cholesterol was 229 mg and the fatty acids 362 mg per 100 cc On these days passed in a diabetic home the carbohydrate was 116 grams, slightly lower than usual during the summer because he was inactive, the insulin 24 units. As stated above his tolerance has continued to rise and with 26 units of insulin he tolerated on December 30, 1928, 166 grams carbohydrate instead of 15 grams as on November 30, 1922

<sup>8</sup>JOSLIN Treatment of Diabetes Mellitus, Loc Cit See Case Indices 3rd and 4th Editions, 1923, 1928

TABLE 7

Case No 632 Male, Onset at 30 years in August, 1912  
Wgt Apr 1916, 57 kilog Wgt Nov 30, 1922, 50 kilog December 1928, 59 kilog  
Height 179 cm

Date	Urine Glucose	Diet in Grams			Total Glucose Grams	Insulin Units
		Carb	Pro	Fat		
1916, April 12	0	26	84	130	88	0
1918, June 24	0	22	74	100	75	0
1921, July 28	0	18	67	87	66	0
1922, Nov 30	trace	15	69	95	65	0
1922, Dec 5	0	41	72	122	95	4 (2-0-2)
1923, May 23	0	43	78	150	103	10 (6-0-4)
1924, May 3	0	38	77	148	98	10 (10-0-0)
1925, May 10	0	46	75	134	103	18 (18-0-0)
1926, May 5	0	70	77	135	128	20 (14-0-6)
1927, June 3	0	122	71	116	175	20 (20-0-0)
1928, June 14	0	135	75	116	190	24 (18-0-6)
1929, Jan 2	0	166	69	119	218	26 (16-0-10)



Case No 1616, Freddie G, "the severest case in a child in the series treated with insulin"<sup>10</sup> and repeatedly cited in former publications developed diabetes in August 1919 at 55 years of age and his state became so pathetic before the discovery of insulin that his parents told me to "do anything you want with Freddie, you can't make him any worse" His weight in July 1919 was 196 kg, but when he came under my observation two months later it was 161 kg, and his height 109 cm Wassermann negative Heredity absent His course is shown in Table 8 At present January 11, 1929, he is a happy boy, weight 323 kg, height 132 cm, and evidently still growing Throughout the winter he does not wear a hat He stands well at school and plays the banjo and mandolin very well With the help of 28 units of insulin his tolerance for carbohydrate has risen from 55 grams in 1920 and probably much less than 36 grams in December 1922 to 128 grams in 1929

Case No 2084, Buddy H, a pale listless child, taking soda and whiskey, came to me

December 1, 1920 with multiple abscesses, and 30 per cent glycosuria which required 72 days of hospital treatment for me to banish Diabetes began 18 months before when he was 3 years and 2 months old He has constantly been under the care of excellent trained nurses, whom he has seen one by one successfully married His weight in December was 11 kg, height 100 cm The weight is now, December 31, 1928, 28.4 kg, and height 127 cm Wassermann negative Heredity absent

In the 12 and 14 days respectively the soda and whiskey were eliminated and the minus carbohydrate balance began to be permanently positive on the sixteenth day of treatment The urinary nitrogen in this period fell from 10.8 and 11.5 grams a day to 4.5 grams With the help of 27 units of insulin his gain in tolerance for carbohydrate has been from 27 grams in March 1923 to 110 grams in December 1928

<sup>10</sup>JOSLIN Jour Metab Research, 1923 2, 651, also Treatment Diabetes Mellitus 4th Ed p 825

TABLE 8

Freddie G, Case No 1616, my severest child diabetic in November 1922  
Age at onset in Aug 1919, 55 years, Weight 161 kilog, Height 109 cm, Weight March 17, 1922, 11 kilog, Weight Jan 1929 323 kilog, Height 132 cm

Date	Urine Sugar	C Gms	Diet P Gms	F Gms	Total Glucose	Insulin Units
1919, Sept 10	0	48	32	24	70	0
1920, March 20	0	30 <sup>1</sup>	61	61	71	0
1922, Nov 3	41%					
1922, Nov 6	19 grams	50	25	35	60	2
1922, Nov 13	6 grams	41	37	50	68	12
1922 Dec 4	0	35	37	68	65	12
1923, March 15	0	36	37	68	65	10
1924 Aug 20	0	41	37	68	70	11.5
1925 May 2	0	44 <sup>1</sup>	50	78	81	14
1926, May 23	0					22
1927, Feb 7	0	101	73	118	150	24.5
1927 Dec 17	5 grams	64	53	93	150	35
1928 June 28	0	101	73	118	150	24
1929 Jan 11	0	128	84	132	160	24 (14 + 10)

<sup>1</sup>Diets not absolutely accurate



TABLE 10

Case No 2560, Billy B Onset at 51 years in June 1921  
Weight March 1922 187 kilog Height March 1922 120 cm  
Weight August 1928 339 kilog Height August 1928 145 cm

Date	Urine Glucose	Diet			Total Glucose Grams	Insulin Units
		C Gms	P Gms	F Gms		
1922, March 22	0	37	35	39	61	0
1923, March 18	0	40	44	82	74	4(2-0-2)
1924, March 3	0	55	95	74	118	14(8-0-6)
1925, Nov 11	0	54	71	107	106	24(12-0-12)
1926, Dec 10	0	63	66	107	112	24(12-0-12)
1927, Dec 30	0	100	64	100	147	24(12-0-12)
1928, Aug 2	0	125	65	125	175	22(12-0-10)

53, and 61 grams respectively and at the recent observation respectively 313, 218, 190, 168, and 175 grams. Insulin is credited with the capacity of metabolizing 15 to 2 grams carbohydrate per unit and rather more than this, perhaps twice as much when a small number of units are administered. In our cases the gains in grams of carbohydrate per unit of insulin were 12, 6.35, 3.1, and 4.0 grams respectively, and in total glucose were 15, 6.43, 4.3, and 5.2 grams glucose per unit insulin. The total gain is not so impressive as the relatively more rapid gain after insulin had been used for a few years. Perhaps the attempt to raise the carbohydrate in the diet should have been made earlier.

Originally just prior to medication with insulin the calories per kilogram body weight were 26, 24, 83, 64 and 34 calories, at present they are 40, 34, 63, 56, and 56 calories. To some extent this meets Allen's contention that if total calories are kept constant the relative proportions of carbohydrate, protein and fat can be shifted indiscriminately. In most of our instances the total calories per kilogram

have been raised and that despite the fact that as children grow older their caloric needs grow less.

How much further should one attempt to raise the carbohydrate of these diabetics? I do not know, but already two have passed the 150 grams mark. I am interested to learn the experience of those who have advocated a high carbohydrate diet. In the meantime I shall forge ahead slowly and observe whether these children and other children can progress as have the two adults. There is no limit set by law to such an improvement.

Again I register the plea that others will record as Brace and I have attempted the course of some of their best patients.

## CONCLUSIONS

1. The clinical course of cases of diabetes of prolonged duration does not show a tendency to increasing severity. Even the careless diabetic may do extraordinarily well.

2. The diabetics of prolonged duration die of the complications of diabetes rather than of diabetic coma which would be their more usual cause

TABLE II GAINS IN TOLERANCE FOR CARBOHYDRATE, TOTAL GLUCOSE AND CALORIES OF FIVE DIABETIC PATIENTS WITH INSULIN DURING 6 OR MORE YEARS

Cases	Observation Preceding Treatment with Insulin			Interval	Last Observation			Gain in Tolerance with Insulin for		Insulin Units
	Carb	Total Gluc	Cal per kilog	Years	Carb	Total Gluc	Cal per kilog	Carb	Total Gluc	
359	58	91	26	6	236	313	40	178	222	15
632	15	65	24	7	166	218	34	151	153	26
1616	30	71	83	9	128	190	63	98	119	28
2084	27	53	54	6	110	168	56	83	115	27
2560	37	61	34	7	125	175	56	88	114	22

if they were approaching a stage of complete diabetes. Insulin refractory diabetics are conspicuous by their rarity in children. The diabetic mortality in children is approaching the vanishing point and in fact is decreasing for all diabetics under the age of 40 years.

3 My diabetic children daily challenge pessimism by their good looks, their vigor of mind and body and their normal sexual development.

4 Failure to demonstrate an increase in carbohydrate utilization by

certain diabetics with insulin may be explained by the excessive calories allowed and the small amount of carbohydrate given over long periods.

5 Five cases of diabetes are reported by the author who show during periods of six years gradual gains in tolerance for carbohydrate varying from 88 to 178 grams with the use of 15 to 28 units of insulin. The gains in tolerance have been greater in the latter half of the period. There appears to be no reason why these gains should not continue.

# Cardiovascular Lesions Following Injury to the Chest\*

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THE superficial position of the heart and pericardium, directly behind the sternum and the adjacent cartilages, exposes them to danger from injuries to the anterior chest wall. With or without injury to the ribs, or even without obvious external bruising, an external blow may produce very serious damage to the intrathoracic structures. Corresponding to the injuries that take place to the lungs, liver, kidneys or spleen in serious accidents, it may be plausibly surmised, the heart will suffer similarly the effects of sudden concussion or compression. The character of these effects will depend upon the status of the heart cycle at the moment of the accident, the resilience and resistance of the thoracic wall, and the form, momentum, and direction of the injuring force. The mechanical process in such accidents is subtle, of course, and the clinical picture often very difficult to solve. It is the milder form of accident that is the more commonly observed and offers real problems of diagnosis and therapy.

Thoracic injuries are generally classified into (1) those confined to the soft tissues (2) those in which the

ribs or sternum are involved, and (3) those which are complicated by injury to the lungs or the heart.

In the present paper, we shall consider the intrathoracic cardiovascular effects produced by direct or indirect violence from without. We emphasize this to make clear our usage of the term "traumatic injury" which we employ in our discussion. Literally, "trauma" means a wound, and its usage should be confined to those occurrences, in which physical violence or mechanical injury is involved, in the production of the lesion. Unfortunately, the word "trauma" has been used in a few published papers in this connection, in the sense of bodily effort involving stress.<sup>1</sup> We believe that its employment in this way is not fully justified.

In cases of heart strain there is no wound produced in the usual meaning of the word. As a result of undue stress or tension the lesion is produced from within the heart or aorta. Heart strain has been clearly defined as an organic condition associated with the sudden development of symptoms referable to the heart and aorta which can be attributed to some unusual mus-

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1. HALL I and FOXES H. W. Trauma as a Cause of Auricular Fibrillation. *Brit. Med. Jour.* 1927 1 p. 359.

cular effort or over-exertion, and which results in physical disability of varying degree and duration<sup>2</sup>

Particular attention also will be paid to the industrial aspects of non-penetrating injuries of the intrathoracic structures, and the considerations that arise in determining the compensation and liability as interpreted by various compensation laws

The principal types of traumatic heart lesions that occur in consequence of direct and indirect violence may be classified under the following headings

#### I Direct Injuries

##### A Contusion and concussion of the thorax

- 1 Injury to the pericardium
- 2 Atrial fibrillation
- 3 Extrasystolic arrhythmia
- 4 Heart block
- 5 Injury to the valves of the heart
- 6 Injury to the aorta
- 7 Injury to the heart musculature
- 8 Rupture of the heart
- 9 Miscellaneous types

##### B Penetrating wounds

- 1 Fatal
- 2 With recovery and post-traumatic effects

#### II Indirect Injuries

##### A From without, such as falls with no direct injury to the chest

##### B Heart strain

<sup>2</sup>KAHN, M. H. and S. Heart Strain in Its Industrial Aspects. Amer Heart Jour., 1928, III, 546

Heart Strain and Its Consequences. Ann Internal Med., 1928, I, 790

Inasmuch as pathological examination of the heart tissue in the milder form of accident to the thorax is not feasible, we can only consider these cases from the standpoint of analogous experimental studies. It is only from the symptoms, and the clinical evidence of disturbance of rhythm, or other functional changes, that we can estimate the extent and determine the localization of the lesions. In severe cases, in which the clinical evidences are marked, or in cases that terminate fatally, an exact discovery of the damage produced is oftentimes obtained by autopsy

Injuries to the thorax are common occurrences in various industries. This applies particularly to all those occupations in which objects are moved about, pulled forcefully out of piles, or thrown from one place to another. Being run over by a vehicle is one of the most frequent causes. An equally frequent accident is the crushing of the chest when a person is caught between two colliding vehicles, or between one such and a stationary object. A hazard also lies in unprotected straps around the wheels of machines. Falling directly to the ground as in tripping is a common cause of thoracic injury. Injury to the heart may also be produced indirectly, according to the natural laws of inertia, when one falls from a varying distance, in which case the force is applied directly to some part of the body other than the chest. Less frequent are the intrathoracic injuries produced by penetrating objects such as bullets, knives, or the sharp fragments of fractured ribs

In some of our group of cases, the

mode of occurrence of the injury to the intrathoracic cardiovascular structures was described as follows

A plank of lumber fell from a scaffold, striking the patient's chest

While pulling at a bag on a wagon its sudden release threw the man backward down to the ground

Tipped and was thrown heavily forward to the ground

Fell down five floors, striking the front of his chest against a pile of boards

A two-ton machine fell upon the patient, throwing him supine

While a heavy bag of coffee was forcefully pulled by means of a hook, it was suddenly released hitting the patient in the precordium

An automobile slipped off its "jacks" on to the patient's chest

While standing the patient fell from a bench striking the front of his left chest against the floor

The handle of a hand-truck struck the man across the sternum

Was struck by a truck

Struck in the chest by burglars

#### CONUSION AND CONCUSSION OF THE THORAX WITH INTRATHORACIC INJURIES

A blow to the region of the heart may cause a contusion of the precordial tissues sufficient to extend to the parietal layer of the pericardium. If this is the full extent of the damage the symptoms may be slight, and complete recovery may follow in a few days. Usually the clinical effects of a contusion are temporary, with faint-

ness, palpitation, and pain, which pass off in a few hours, or endure several days. In such cases, followed by recovery, no subsequent danger exists, and the patient may be considered well as soon as the effects have passed off.

But, in some cases, the effect of the injury is not localized to the mural tissues. As the thoracic wall is markedly yielding, a severe blow or sudden compression may momentarily alter the shape and volume of the intrathoracic space. Such a distortion may involve a displacement of the heart and mediastinum, and may be very severe producing the symptoms of shock and even resulting in death. This may happen with surprisingly slight or even with no evidence of external injury to the thorax. The possibility of visceral injury should, therefore, always be kept in mind, even when the initial symptoms are mild in character. The particular evidences of cardiac affection, in such cases, lie in the development of arrhythmias, recurrent dyspnea, palpitation and pain after exertion. Such cases come especially into notice when the questions of disability from work and liability for compensation are considered.

In severe cases, which are often spoken of as concussion of the chest, the patient may become unconscious and go into shock. The face is pale, the pulse weak and imperceptible, the respirations are shallow. Eventually a fatal issue results. Trauma in the region of the lower portion of the thorax, near the heart and diaphragm, is followed by greater shock than in more remote regions of the chest.

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The prognosis in thoracic contusions depends upon the character of the injury. In cases associated with marked shock, the outlook is always grave.

The medico-legal questions involved in these cases often present no little difficulty for their satisfactory solution. To illustrate the obscure clinical effects often produced by direct violence to the chest, and the practical importance of these cases from the standpoint of the ensuing disability and the compensation liability, the following group of cases is briefly summarized.

In the following case, although cardiac damage would be anticipated from the severity of the accident, none was found. Disability due to cardiac injury was the patient's claim.

Louis H., a robust mechanic aged 45 years, was lying on his right side repairing the rear end of a heavy automobile bus. The latter slipped off the "jacks" supporting it, pinning down the patient's arms and chest. The bus was raised promptly and the patient released. He was not unconscious, was able to walk about, but felt a diffuse soreness across the front of the left chest, and pain along the right costochondral junctions. The next morning he was admitted to a hospital, where he remained abed for seven weeks with some improvement. X-ray at the hospital showed no evidence of fracture or pulmonary injury.

Eight months after the accident, he still felt soreness in his chest after straining, lifting or pulling, and even when at rest. Occasionally he had a sensation of tightness across the midsternal region and to the left side of the median line. He had no severe attacks of radiating pain, and no pain in the back of the chest or in the arms, and suffered no cough or other respiratory symptoms.

Physical examination, eight months after the accident, showed a heart rate of 86. The left border was within the nipple line,

and the apex beat was distinctly visible in the epigastrium. Over the apex, and in the epigastrium, there was palpable a slight systolic thrill. The muscular quality of the first sound was fair. Over the pulmonic area, there was a faint systolic cardio-respiratory murmur. The basic sounds were not accentuated. The blood pressure was 156/90.

*Summary*—It is of particular significance in this case that there were no active symptoms referable to the heart or intrathoracic viscera immediately after the accident. It is presumable that if there were injuries to the heart as a result of the accident, immediate symptoms would have developed.

In this case, the chest was cushioned against the compressing weight by both arms. The thoracic wall yielded at the right costochondral junction as a result of the compression, producing localized pain along this line. The feeling of tightness and soreness across the chest that the patient felt after straining may have been due to the mural thoracic injury.

There is doubtless causal relationship between the accident the patient suffered and the symptoms he complained of.

In the following cases, injuries of varying severity to the chest occurred, but with no definite evidence of intrathoracic cardiovascular injury or aggravation.

The case recorded below portrays the obscurity of the effects of direct blunt violence to the front of the chest.

Madeline F., a little woman of 33, weighing only 82 lbs., slipped and fell forward striking her breast bone against the corner of a table. She had immediate, very severe, localized, cramplike pain in this region and



felt rapid palpitation, without irregular action. She went to bed immediately. The pain gradually lessened in severity, but there persisted for at least six months thereafter, a continuous sensation of heaviness and pressing pain in the mid-sternal region. Dyspnea and palpitation on exertion were also present. The disability was mainly attributed to the sternal pain.

Examination of the heart revealed a short, rough, rumbling systolic murmur localized over the apex, and another soft blowing murmur was heard to the left of the manubrium. There was extreme tenderness over the sternum and xiphoid, and adjacent left costal cartilages. Physical examination was otherwise negative. No fractures of the sternum or ribs were present, and x-ray of the heart revealed no significant findings. The electrocardiogram was equally uninformative.

*Summary*—Six months after the accident, we note, in this case marked precordial and sternal tenderness, dyspnea, palpitation on exertion, an apical murmur, and disability due to sternal pain. It is difficult to say exactly what the pathological process was that produced the patient's symptoms and disability so long after the accident. But that small foci of mediastinal damage may develop in such a case is well recognized.

Jeremiah McC, an auto mechanic aged 55, was struck by the fender of a suddenly propelled truck in the region of the left lower ribs and left groin. When he regained consciousness he found himself seated against a fence to which he had been carried. He had intense pain in the left lower abdomen and an aching numb sensation in the left hypochondriac region. There were no abrasions of the skin, no ecchymoses, and no bleeding from any part of the body. He had no cough or hemoptysis, no vomiting, melena or hematuria. He returned home by trolley, walking two blocks without assistance, and went to bed. That night the sharp localized pain in the left

lower ribs became worse, especially on deep breathing, and there was some local tenderness. He felt dyspneic, especially in the recumbent posture, and had palpitation at times. Two days later, pleurisy was diagnosed.

One month after the accident, the patient had a sudden severe localized gripping pain over the left lower ribs considerably below the region of the breast. He did not faint but was relieved by hypodermic medication. Similar attacks of momentary pain recurred, not radiating to the arms, neck, or chest, with pallor and cold sweat followed by palpitation. He had slight dyspnea and palpitation on moderate exertion and was unable to breathe easily in the recumbent posture. The tenderness over the ribs finally disappeared.

Physical examination four months after the accident showed the left border of the heart just outside the nipple line, 10 cm from the median line. The right border percussed 4 cm from the median line. The apex beat was palpable in the fifth and sixth spaces in the nipple line. The sounds at the apex were good and the basic sounds were normal. There were no murmurs and no tender spots on the chest wall. There was an area of pain over the fifth and sixth left interspaces corresponding to the region of the heart apex. The blood pressure was 122/70. There was no evidence of pleural affection. The electrocardiogram showed a rate of 66 and was otherwise negative.

One year after the accident the patient appeared in good condition and had for a length of time, not had any further attacks of pain or discomfort in the chest. He still claimed some disability on account of the shortness of breath, but clinical evidence did not indicate any further disability from the accident.

*Summary*—In this case the injury produced apparently no permanent affection of the heart, although the symptoms and the attacks that the patient suffered from may be attributed to some direct trauma to the heart. The x-ray showed fibrotic pleb

the right upper lobe, but there was no evidence of aggravation of this condition

James J. F., an old watchman, was attacked by burglars, beaten, bound, and gagged, and was struck in the left side of the chest. He was taken to the hospital with broken ribs and fractured knees.

Cardiovascular examination showed evidence of arteriosclerosis, with marked tortuosity, hardening, and calcification of the larger and smaller peripheral vessels. The heart presented effects of these arterial changes with frequent irregularities, due probably to auricular premature beats.

*Summary* — The arteriosclerotic process in this case was, of course, the result of senescence. It was important to decide, if possible, whether the assault in any way aggravated this condition. Obviously, it could not have affected the general arteriosclerosis. Whether the direct injury to the chest wall, producing fractured ribs caused some myocardial damage is problematic.

#### *Involvement of the Pericardium*

The pericardium may react to a contusion or concussion of the chest with the development of acute pericarditis. This is often fibrinous in character, and often with slight effusion. Pericardial injury may develop following a sudden fall or lurch forward in which the chest is struck against a projecting surface or edge. A blow to the chest by a mallet or a fist, as in boxing, may be the history.

Generally six to twelve hours intervene before an indication of pericardial involvement manifests itself by sharp, stabbing pain in the precordium, a slight rise in temperature, associated with tachycardia and pain in

breathing. The symptoms of traumatic pericarditis are not particularly different from the condition in its more usual clinical form. Important, however, are the history of direct injury, and the shorter duration of the clinical course in the typical or mild cases. Recovery may take place without pericardial adhesions. Often, however, the symptoms linger for a longer time, the patients complaining of some dyspnea and palpitation and tenderness over the precordium. In such cases, further unrecognized damage may be suspected.

Accidental traumatic pericarditis has to be differentiated from that form which occurs in an attack of sudden coronary closure or so-called stenocardia. In the latter, an aseptic local pericardial reaction takes place on the visceral pericardial surface, with the development of mild effusion, which also subsides within a short time. In such cases, however, the correlated advanced coronary lesion, and the symptoms of angina pectoris are part

in a state of shock. Laparotomy was performed, but no cause for the symptoms was found. There was very little free fluid and no exudate. Breathing continued difficult and painful. The patient now also complained of precordial pain radiating to the shoulder. Finally, on the third day symptoms of pneumonia were manifest. They increased in severity rapidly and the patient died that night. At autopsy, a rent, 2.5 cm long, was found in the apex of the pericardial sac—with no fluid in the sac itself. The neighboring organs were not injured by the fall.

The following case under our observation presents the question of pericardial involvement.

Edward A. K., aged 49, tripped and was thrown heavily forward to the ground. Later in the day, he felt some tightening in the chest and had a little difficulty in breathing. That evening he complained of shortness of breath which became worse the next day. He remained in bed for a month after the diagnosis of acute pericarditis was made.

Physical examination a month later showed marked dyspnea, with a slow pulse of small volume. The heart sounds were somewhat muffled. There was no evidence of endocarditis and no symptoms or signs to suggest myocarditis. The lungs were negative and the liver was not enlarged. About five months after the accident, cardiologic examination showed the heart to be moderately enlarged with the right border  $4\frac{1}{2}$  cm and the left border 11 cm from the median line in the fifth space. The apex beat was not visible nor distinctly palpable and was heard best in the fifth space inside the nipple line at a regular rate of 78 per minute. The second aortic sound was slightly accentuated. The brachial arteries were somewhat tortuous and the blood pressure was 140/95.

The electrocardiogram showed normal sinus rhythm, left ventricular preponderance

inversion of the T wave in lead I and the P wave iso-electric in lead III. Teleroentgenogram showed the heart enlarged to the right and left, with definite hypertrophy of the left ventricle. The ascending aorta was not dilated.

The claimant resumed lighter work for five months or more before he died rather suddenly. He had not consulted a physician for these five months prior to his death.

*Summary*—There is definitely a history of an accident to the chest followed promptly by cardiac symptoms and the development of pericarditis. Whether or not the co-existence of acute coronary closure figured in its production must remain speculative. Five months after the accident, there was enough indication in the cardiac enlargement, hypertrophy of the left ventricle, dilatation of the ascending aorta, arteriosclerosis in the aorta and changes in the electrocardiogram from which to conclude that there was some pre-existing affection of the heart. Yet after the death of the claimant and from the available data one cannot escape the suspicion that as a result of the accident there was injury to the heart which produced pericarditis and that it was not due to coronary involvement *per se*.

### *Atrial Fibrillation*

It is well known that bodily effort or physical stress may produce atrial fibrillation (1). In these cases the onset in point of time is clearly defined immediately following and definitely associated with unusual labor.

But the literature is very scant concerning instances of atrial fibrillation that follow direct violence to the chest. What the pathological changes are that produce this condition is

cannot declare with certainty. However, the possibility of subepicardial ecchymosis in the auricular muscle must be considered. The cardiac damage in these cases is not disputable. The symptoms produced by its development are quite conspicuous, promptly causing more or less total disability. It is known that fibrillation diminishes greatly the cardiac output, as a result of which, symptoms of deficient cardiac function develop.<sup>5</sup> Dyspnea, palpitation, occasional sticking pain in the precordium or just below the left breast as well as the development of cough due to pulmonary stasis, and edema of the legs.

The accidental occurrence of auricular fibrillation will go on to spontaneous recovery in a short time, or to recovery following a period of rest and the use of special medication, or to recurrence with the persistence of the heart condition. In fact, once established, auricular fibrillation has a tendency to recur or even to become permanent.

Levison reports the case of a truck driver, aged 20, who was caught between two trucks and rather severely crushed in the thoracic region.<sup>6</sup> He was not rendered unconscious, and there were no fractures determined by the x-ray. There was no external wound, cut, or laceration, except a few discolorations from bruising. The patient complained of severe pain in the thorax generally, and of marked distress in the cardiac region with breathlessness. He was not cyanotic. Ex-

amination showed definite auricular fibrillation. The heart rate was 150 per minute, with marked pulse deficit. There was considerable tenderness over the chest region generally. The pupils of both eyes were dilated. The patient was weak, but clearly conscious and able to speak without any trouble. Deep breathing or any movement was difficult. The auricular fibrillation persisted for twenty-four hours. It is regrettable that an electrocardiogram was not secured during these first few hours. When it was taken thirty-six hours after the injury, it showed the P-R interval and the QRS complex normal, with slight sinus arrhythmia, and normal rate. The T waves in leads I, II, and III were abnormally large. There was definite left ventricular preponderance. The heart action seemed to be clinically normal at this time. The patient still complained of considerable pain in the region of the thorax and back, but the sense of cardiac distress and breathlessness had disappeared. When the patient had finally apparently recovered, physical examination of the heart revealed no evidence of any cardiac disease.

Illustrating this type of occurrence, is the following case which has been under our observation for some time.

Joseph G., a tall, well-nourished young carpenter aged 33, was struck across the front of his chest, as he was looking up by a plank of lumber which fell on and from a building scaffold, 18 feet from the ground. He fell backward, momentarily dazed, stood up for a few minutes, feeling very weak and leaning against the building for support. There was diffuse soreness in his chest and he "breathed hard as if all out of wind." He then continued light work with intervals of rest. When working, he felt weak and dizzy, and "faint"

<sup>5</sup>EASTER AND SWARTHOLT. Quoted by Hay and Jones. Loc cit.

<sup>6</sup>LEVISON. L. A. Ann Int Med., 1927, 1, 225.

in his gait. He worked half of the following day. During two weeks of hospital observation, he felt weak with pressing pain across the front of the chest.

Three months after the accident, his heart showed no enlargement and no murmurs, but showed rapid auricular fibrillation and a low blood pressure—104/78. There was no evidence in the history and in the physical examination of any previously existing heart condition. X-ray examination was also negative. The electrocardiogram showed coarse auricular fibrillation and tachycardia, but no ventricular preponderance and no indication of any pre-existing valvular disease. After a preliminary period of rest and digitalis medication, the patient was given three grains of quinidine sulphate every three hours for several days. There occurred quite remarkable improvement, with resumption of normal sinus rhythm. The symptoms promptly disappeared. The patient was able to walk about with progressive improvement and increasing strength, so that six months after the accident, recovery was quite complete.

*Summary*—In this case, cardiac symptoms, including the feeling of distress and soreness across the front of the chest, followed immediately upon the recorded accident. In point of time, the onset is therefore clearly and directly associated with the injury. We therefore believe that the condition of the patient had a direct relationship to the accident. There were not present in the history or physical examination any of the other causes which might induce auricular fibrillation such as rheumatism, syphilis, arteriosclerosis, Graver's disease or any other toxic causes. There was no valvular lesion or cardiac changes incidental to a lesion such as hypertrophy, accentuation of the basic sounds or ventricular preponderance in the electrocardiogram.

The pathological changes that may have taken place from the injury are necessarily speculative. The possibility of subepicardial ecchymosis in the auricular muscle is to be considered. The process takes a long time to heal and therefore the auricular fibrillation may last an indefinite period of time.

The electrocardiograms taken in this case are of interest. (See Fig 1.)

During the preliminary period of observation, the electrocardiographic records showed rapid, coarse auricular fibrillation with an average rate of 150 per minute. There was an indication of left ventricular preponderance. Premature beats occurred singly or in groups arising probably in the auricular wall in the region of the A-V node. Such a group is shown in lead II of the first portion of the tracing.

Two weeks after sinus rhythm had been restored and the effect of digitalis had worn off the electrocardiogram showed a rate of 75 per minute. The left ventricular preponderance and the general voltage were of course unchanged. No premature beats occurred. The T wave was slightly taller in leads I and II and was distinctly inverted in lead III. The P wave was rather sharp and there was a suggestion of its being notched.

A few months after the patient had been without medication the electrocardiogram showed the T wave to be a little more inverted. This electrocardiogram is shown in the last portion of the record.

Patrick C. was the chief clerk of the hospital. While striving to put a book on the shelf, he was taken by a stroke of the heart.

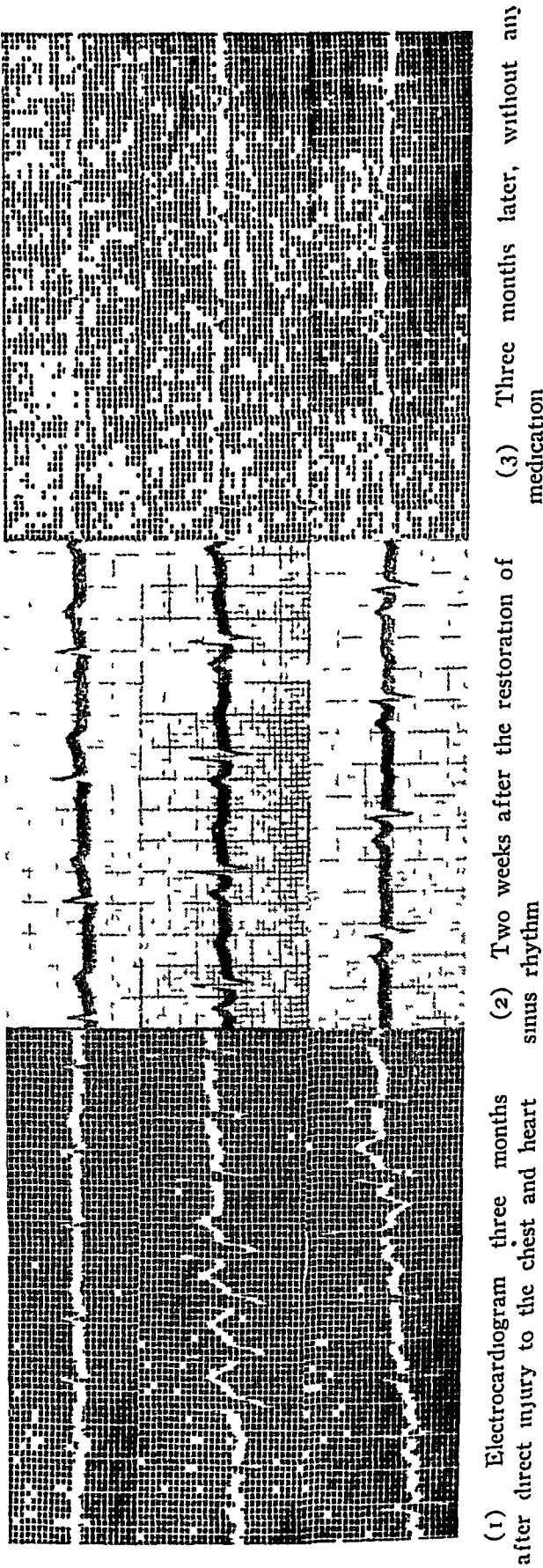


FIG 1—Joseph G

slipped out, and the claimant fell, striking his chest on the end of the wagon, and falling on his back to the ground five feet below. He was unconscious for a few minutes, but continued his work after that, delivering cases elsewhere. He then returned home, stayed in bed two days, worked one day thereafter, and then remained under the care of a physician. He became steadily worse and was admitted to the hospital four months later.

Examination at that time showed his heart to be enlarged. The apex beat, in the nipple region, was absolutely irregular, with auricular fibrillation. The muscular tone of systole was of poor quality. There was a loud blowing, systolic murmur at the apex and over the precordium. The radial, brachial, and temporal arteries were very hard and tortuous. The lungs showed a moderate amount of pleural effusion at both bases. This re-accumulated at intervals, necessitating frequent aspiration, with only temporary benefit. The auricular fibrillation persisted and the myocardial failure progressed, so that the patient died with pulmonary edema and advanced heart failure five months after the accident.

*Summary*—The patient showed arteriosclerotic myocardial disease and auricular fibrillation. If the fibrillation had existed prior to the injury the man would have had some distress or inability to do his work. In the absence of this we are compelled to attribute the onset of the fibrillation to the direct trauma to his chest that he suffered in the fall. Although no roentgenograms were available clinically it appeared that there had been traumatic fracture of some ribs. The auricular fibrillation could very well have resulted from the accident and death from the myocardial failure was correctly adjudicated the result of the aggravation of the heart condition produced by the accident.

Mary McN was a janitress 39 years of age. She fell headlong down a flight of fourteen steps, striking the top of her head against the wall at the landing, and twisting her neck. She did not faint or become unconscious. The following day she felt sharp shooting pain radiating from the scapular region up over the front of the chest and into the neck. The pain was aggravated by deep breathing, but not by moving about. Her family physician prescribed digitalis, and she remained abed for ten days.

Nine months after the accident, the patient complained of nervousness, fatigue, and exhaustion. She had rapid, severe palpitation, and a choking sensation on ordinary exertion, such as making beds or sweeping. There was also marked shortness of breath, especially on exertion. She had to sleep high on pillows to avoid a smothered feeling. She of course was unable to work.

Physical examination nine months after the accident showed the heart to be considerably enlarged to the right and left. The apex beat was forceful and palpable in the fifth space. There was also a palpable pulsation to the right of the lower sternum which was visible in the epigastrium. Over the apex there was a marked systolic shock with a presystolic thrill. There was a short rumbling pre-systolic murmur audible over the apex, crescendo in character preceding the systolic shock. The pulmonary second sound was accentuated.

During an examination one day the heart action was absolutely irregular in force and rhythm due to auricular fibrillation. The rate was between 140 and 150 per minute. There was a suggestion of a presystolic thrill. The murmur was diastolic short and blowing in character and audible only during the longer pauses between heart beats. During re-examination on the following day the heart action was forceful and showed the presence of murmur preceding heart beats but no fibrillation.

The blood pressure was 115/92-112/72, on two different occasions. The heart was slightly protuberant and enlarged. There was slight peripheral edema and the veins were present in the neck.

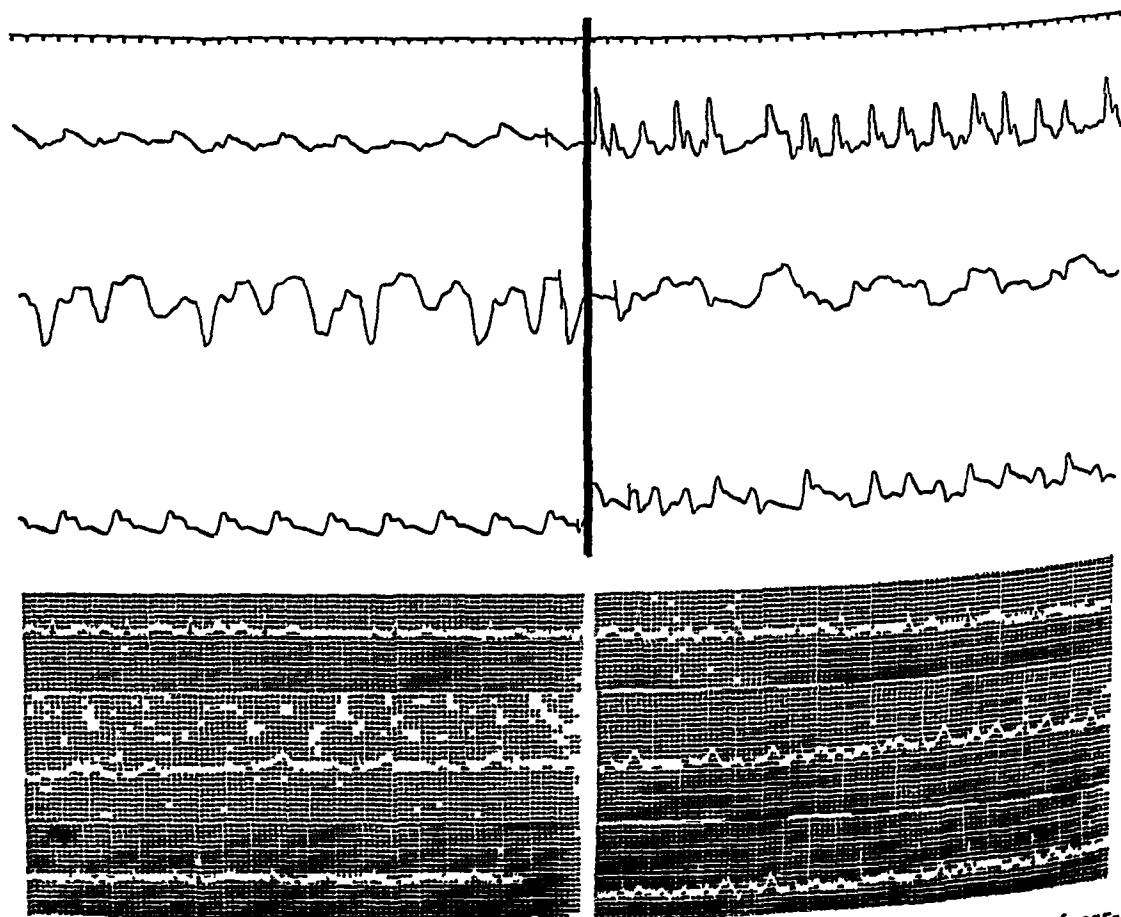
Teleroentgenographic studies showed the heart to be enlarged in its transverse and longitudinal diameters, and revealed the presence of mitral valvular disease

Polygraphic tracings during the attack of fibrillation showed a rapid irregular radial pulse with the absence of the auricular wave in the jugular tracing. There was a suggestion of a presystolic thrill in the cardiogram. Another tracing, taken two days later, showed only the presystolic wave in the cardiogram due to mitral stenosis (Fig 2)

The first electrocardiogram showed very rapid auricular fibrillation and low voltage. There was also an occasional nodal premature beat. The *T* wave was upright in all three leads. The subsequent electrocardiograms showed slight sinus arrhythmia with the occurrence of auricular premature beats. The voltage was low and the *P* wave was

notched and wide in lead II and inverted in lead III. There was no evidence of ventricular preponderance (Fig 2)

*Summary*—The patient had advanced chronic rheumatic mitral stenosis and regurgitation, with the occurrence of auricular premature beats and attacks of paroxysmal auricular fibrillation nine months after the accident when she first came under our observation. The heart was dilated and there was an old-standing congestion of the liver. The physical signs and the suggestive fact that digitalis medication had been prescribed promptly after the accident by the patient's family physician point to the previous existence of the valvular



(1) Polygraphic and electrocardiographic tracings showing normal sinus rhythm

(2) The same during an attack of paroxysmal auricular fibrillation.

FIG 2—Mary McN



lesion. That there was aggravation produced by the fall is suggested by the increased disability, the progressive orthopnea, the inability to climb stairs, and the enlargement of the liver and edema of the legs.

The natural progress of chronic rheumatic mitral stenosis and regurgitation eventually leads to symptoms and signs which would have produced the clinical picture found by us. The increase of her symptoms may have been due to such a gradual process. It thus becomes difficult to decide whether the alleged accident produced aggravation of her condition. There is no indication of any sudden and immediate heart affection resulting directly from the accident. There is no evidence that the patient developed an attack of auricular fibrillation soon after the accident, we therefore cannot attribute any direct relationship between this phenomenon and the patient's fall. The electrocardiogram shows no evidence of myocardial disease that might possibly be attributed to any trauma.

Permanent aggravation due to accident may result from a traumatic organic change in the heart. There was no evidence in this case of any direct violence to the chest. There is no evidence that the fall and fight produced immediate fibrillation from indirect effects.

The patient had temporary disability due to her accident on account of skeletal injuries. Her disability nine months later, however, was due to her chronic rheumatic heart disease and not to any residual aggravation from the accident.

### *Extrasystolic Arrhythmia*

Perhaps the most frequent form of irregularity of the heart action that takes place is that known as extrasystolic arrhythmia, in which premature beats interrupt the normal heart rhythm. These may arise in the auricle, or at any point in the ventricular musculature. The usual cause for their occurrence is focal myocardial irritation at one or more points, due either to rheumatic inflammation, or to coronary changes. A less common cause for their occurrence however lies in the lesions produced in the cardiac tissue by heart strain by direct injury from blunt violence such as blows to the chest or by indirect injury, as in falling from a height.

Where trauma is under consideration as a cause of this form of irregularity, it may be held liable by the process of exclusion. In young people, toxic and infectious causes have to be eliminated as possible factors. In older people arteriosclerosis usually complicates the picture. It is, therefore the clinical relationship between the accident and the development of this form of irregularity that guides us to the establishment of a causal association.

The symptoms of extrasystolic arrhythmia are often not pronounced. Usually there is a sensation of a sudden interruption of the regular action of the heart "as if the heart suddenly turns over," "a short thump in the chest followed by a pause," etc. There may be a feeling of momentary choking, faintness or dizziness or darkness before the eyes, particularly if two or more extrasystoles follow in succession. Extrasystolic myocardial pain may be

associated tinge of momentary pain. The occurrence of this form of irregularity of heart action and the locus of its origin in the cardiac musculature are determined by means of the polygraph and electrocardiograph.

Extrasystoles may recur for years, or they may subside after a short period of time. In older people with arteriosclerotic coronary changes, traumatic extrasystoles are more prone to persist than in young individuals. In some cases, quinine sulphate produces beneficial effects. When extrasystoles are frequent, total disability may result. They often prevent an individual from doing strenuous work.

The following case serves as an example in which the consideration of this condition comes into play.

Gustav E. A., was a machinist and iron worker, 64 years old, who fell a distance of five or six floors (75 to 80 feet) upon a pile of boards, striking the front of his chest and fracturing several ribs. He was unconscious for a few minutes. There was no hemoptysis. Following the accident, he at times had pain in the back of his right chest. He had never fainted and had no anginal attacks. There was slight dyspnea and palpitation on exertion and there developed slight edema of the legs.

Physical examination two years after the accident showed the heart slightly enlarged to the left. The sounds at the apex were clear. The aortic second sound was slightly accentuated. There were frequent ventricular premature beats and occasional short paroxysms of a series of six to ten premature beats which, by the electrocardiogram were noted to arise at the apex of the right ventricle apparently at two different foci. The brachial and radial vessels were tortuous, and their walls thickened and sclerosed. The blood pressure was 194/120.

The electrocardiogram showed left ventricular preponderance. The P wave was

diphasic in lead II. The T wave was low in lead I and isoelectric in leads II and III (Fig. 3).

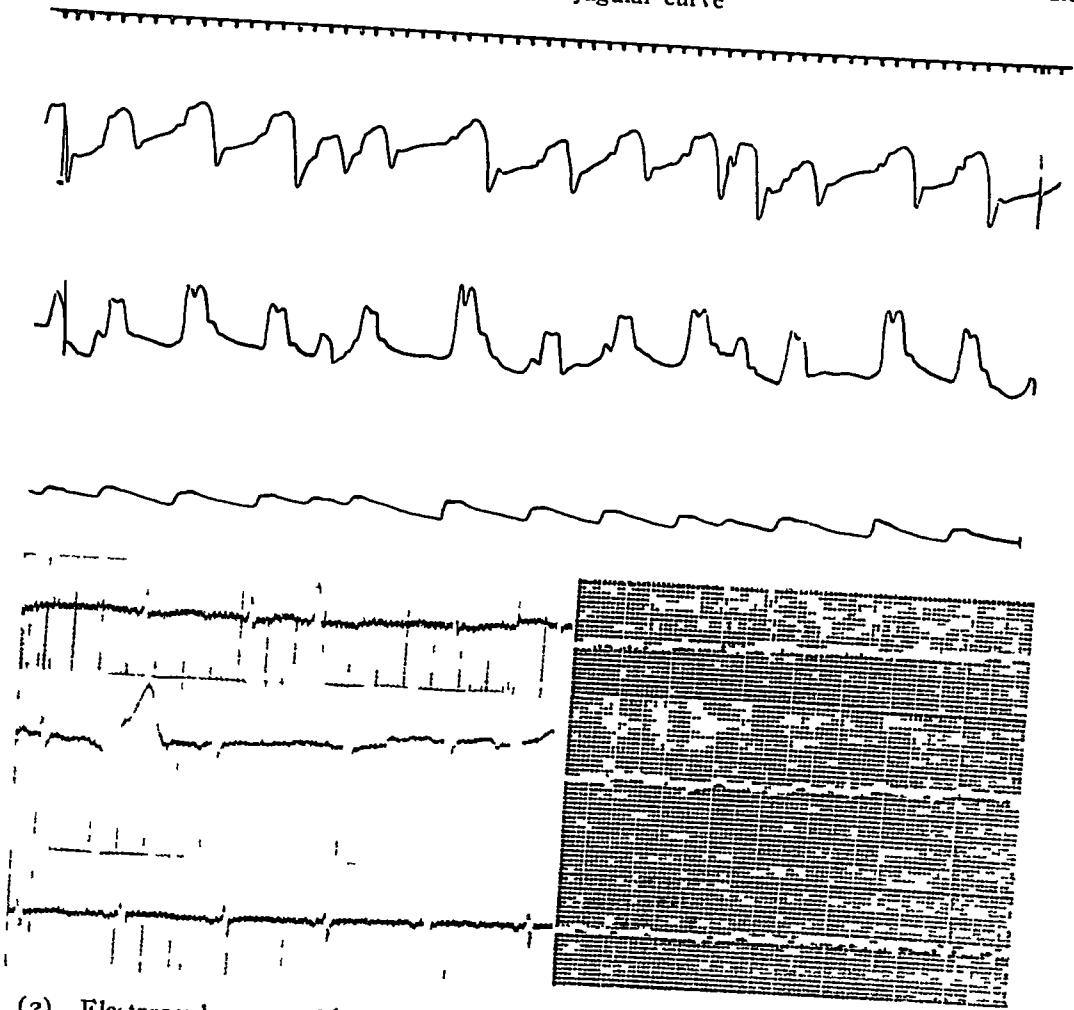
One year later, the patient became worse, showing increased pretibial edema. The heart became markedly enlarged. The apex beat was in the fifth and sixth spaces, outside the nipple line. The left border was within the anterior axillary line. The blood pressure was 192/100. No extrasystoles were audible. The electrocardiogram was little changed, but for the absence of extrasystoles.

*Summary*—The patient suffered from extrasystolic cardiac irregularity which was discovered after direct injury to his chest. The fact that he was able to do hard work previous to the injury indicates a previously good circulation. His arteriosclerosis was associated with his age and may have been contributory to the cardiac irregularity, or may even have been wholly responsible for it. Nevertheless, the severity of the direct injury to the chest makes it almost unreasonable to exclude direct trauma to the heart as a related cause of extrasystoles. No one can gainsay that the injury was a factor in causing the extrasystoles and the consequent, more or less permanent disability of the claimant.

### *Heart Block*

The location of the trauma in the myocardial structure will predicate the functional disturbances or arrhythmias that may develop. Cases of heart block have been reported from direct injury to the chest. Of course, in penetrating wounds, the effect of injury in the region of the bundle branches produces clinically what in the physiological laboratory is recognized as the Erlanger ligature. But the condition of heart block may follow

(1) Polygraphic tracings showing the frequent extrasystoles, and trapezoidal cardio-gram, and the presence of the "a" wave in the jugular curve



(2) Electrocardiogram 2 1/2 years after direct injury to his chest

(3) The same 3 1/2 years after the injury

FIG 3—GUSTAV F. A.

ma to the precordium without any penetrating wound, or even with no obvious injury to the thoracic wall

Rosenson reports a case of temporary partial heart block in a boy aged 10 1/2 years who had received a hard fist punch over the precordium. Following the blow he complained of weakness and a peculiar fluttering sen-

sation over the region of the heart. He was unable to walk, felt faint and was carried to bed. Two days later on attempting to walk he fell and was unconscious for a few minutes. Two weeks after the injury to his chest he still suffered slight dyspnea on exertion. The heart showed no enlargement. There was a pulmonary systolic murmur functional in character. The sinus rate was 120. The electrocardiogram showed a normal sinus rhythm.

"ROSENSON, W. Heart Block in a Child Following Trauma to the Precordium. Amer Jour Dis Children 10:4 MAY 1931

heart block with a rapid auricular rate. The T wave was inverted in lead III. The conduction time was 0.28 of a second. Within a month after the accident, with rest in bed, the child made a complete recovery. The electrocardiogram indicated a return to normal rhythm.

The pathological process that developed in the conduction system following the blow to the chest wall is conjectural. It may have been a slight hemorrhage in or about the node of Tawara, or a functional change in the intracardiac nervous mechanism.

### *Injury to the Valves of the Heart*

Injury to the front of the chest, with or without injury to the ribs, or even without obvious external bruising, may cause rupture of one of the valves in the heart. The causes noted are blows on the front of the chest, compression between wagons, kicks, and falls from a height. With the increase of automobile casualties, valvular injury is not infrequently the result of accidents in traffic.

Rupture of an aortic or mitral valve may be produced experimentally by smiting the walls of the thorax in animals, or in the cadaver.<sup>8</sup> In the reported experiment on the cadaver by Potain and his co-workers, artificial hydrostatic pressure through the aorta caused rupture of the aortic cusps with a pressure varying from 116 mm Hg to 484 mm Hg.<sup>9</sup> Artificial hydrostatic pressure in the left ventricle

produced rupture of the chordae tendineae by a pressure of 1050 mm ( $1\frac{1}{2}$  atmospheres), and of the flaps by 184 mm, and heart rupture by 896 mm. After the aorta was filled with water to give normal blood pressure, a sudden blow on the upper chest produced tears of the aortic cusps. The force of the blow raised the aortic blood pressure from the normal 120 or 150 to 170.

These lesions have been known to occur clinically in consequence of external injury to the thorax. This may occur in a heart and valves altered by disease, as well as in valves previously healthy. Senac, in 1778, was the first to discuss traumatic rupture of the valves, and he cited three cases.<sup>10</sup> Thirty years later, Corvisart amplified our knowledge of the subject, and since then a great number of clinical and pathological reports has accumulated.<sup>11</sup>

In the mechanism of such an accident, the external blow violently compresses the thoracic cage. The glottis may be closed in deep respiration, and the thorax held rigid. We may conceive of a violent concussion of the distended aorta just at the moment of full ventricular systole. Under such circumstances, rupture of an aortic cusp might take place. In cases of rupture of the mitral valve, on the other hand the blow must have fallen upon the heart in diastole with the ventricle filled with blood. The sudden increase in ventricular pressure produced against the closed and re-

<sup>8</sup>POTAIN. Clin. Med. de la Charité, Paris, 1894.

<sup>9</sup>BARIEF. Recherches sur les Ruptures Valvulaires du Cœur. Rev. de Med., 1881, 1, 132.

<sup>10</sup>SENAC. Traité des Maladies du Cœur. 1778. Vol. I.

<sup>11</sup>CORVISART. Essai sur les Maladies du Cœur. 1811.

sisting, thin mitral valve may tear it across or away from the chordae tendineae, or even from the papillary muscles. There are cases reported in which simultaneous rupture by violence was found to have involved both valves.

In the history of some of these accidents the distinction between outer and inner stress can be made only with difficulty. Thus, when an individual like in the case recorded below, resists the attack of burglars who have pinned his arms and beaten his chest with blows from their fists he may have sustained heart injuries from the direct violence, as well as from the stressful effort of his resistance. But, probably the mechanical process of the production of injury is similar in both cases, force exerting itself from the suddenly increased pressure in the aorta against a filling and stretching left ventricle.<sup>2</sup>

Rupture of a cusp of the aortic valve is much more common than of the mitral valve in cases of direct trauma to the anterior chest wall. Perhaps one of the reasons lies in the anterior position of the aorta which renders it more exposed to the effect of direct concussion. Peacock collected 17 cases in which one or more of the aortic crescents was ruptured in this way.<sup>12</sup> Wilks recorded the case of a youth of 19 in which a blow to the chest, an accident such as might happen in boxing, ruptured the posterior cusp of the aortic valve from its free

margin to its base.<sup>13</sup> In Daganello's case, a healthy man was crushed between a cartwheel and a post.<sup>14</sup> He continued work the same day, but the next day he was unable to exert effort without the onset of dyspnea. Little by little, he grew worse with cyanosis and pulmonary stasis. There was also an aortic diastolic murmur. Autopsy, six months later, revealed dilatation of both cardiac cavities and hypertrophy of the left ventricle. The healthy aortic cusps were found completely torn away from a healthy aortic wall. Colwell and Mark published the case of a man, aged 20 who fell from a scaffold three weeks after he had a negative physical examination of his heart.<sup>15</sup> On re-examination ten days after the accident he had a double aortic murmur, Corrigan pulse and enlargement of his heart toward the left.

Barie gives thirty-eight cases of traumatic aortic injury.<sup>16</sup> He records thirteen cases of rupture of the valves of the heart by external violence without external wound including eight cases of rupture of the aortic cusps and three of the mitral valve. As some of these cases are very typical they are briefly abstracted here:

1. A healthy laborer 45 years old fell a distance of 15 feet striking his left chest against a hard pavement. There was ecchymosis of this region for sev-

<sup>12</sup>WILKS, S. Trans. Path. Soc., London 1865, vol. 77.

<sup>13</sup>DAGANELLO. Arch. Med. et Chir. Paris 1908, 1, 710.

<sup>14</sup>COLWELL AND MARK. Rupture of the Aortic Valve. Brit. Med. Jour. 1901, ii, 1730.

<sup>15</sup>PEACOCK, T. B. On Some Causes and Effects of Valvular Disease of the Heart. J. Churchill & Sons, London 1865. Page 34.

eral days, but no fracture of the ribs. He was disabled and in bed. Eleven days after the accident, he developed severe precordial pain and palpitation. Dyspnea developed and increased, and within two months edema of the legs developed. The heart became hypertrophied, its action heaving, with a very loud diastolic aortic murmur. The influence of the traumatism in the production of the lesion in this case is unquestionable. The trauma produced rupture of one or more of the aortic cusps.

2 A healthy man of 35 was struck in the left chest by the head of a comrade. He lost consciousness immediately, and soon began to feel a constant oppression in the chest, dizziness on even slight exertion, dyspnea, and palpitation. He developed marked signs of aortic insufficiency.

3 A boy of twelve fell from his horse, landing with outstretched arms on the ground. He developed signs of cardiac disease and died with cardiac failure. At autopsy, a distinct notch was found in one of the aortic cusps, the location of a tear resulting from the accident.

Heidenhain reports the case of a healthy sailor, 49 years old, who was struck in the chest by an anchor which he was hoisting.<sup>10</sup> He immediately had severe pain in the chest but continued at moderate work for one week. The pain persisted, dyspnea and pal-

pitation after exertion developed, and after six weeks, the patient took to his bed. At times, the attacks of palpitation occurred even during rest. At that time the heart was considerably enlarged both to the left and right, with epigastric pulsation and mild arrhythmia. A loud systolic murmur and a soft diastolic blow were heard over the aortic area and also at the apex. The diagnosis was made of aortic stenosis and regurgitation. In this case, the sailor suffered no previous cardiac condition, as his work had always been so strenuous. The likelihood of a traumatic aortic lesion produced by contusion of the chest was accepted by the author.

Peacock reports the case of a previously healthy dock labourer, age 36 who was pulling with other men at a sugar hogshead, his hand slipped and struck him a severe blow on the left side of the chest, and he fell backwards.<sup>12</sup> He immediately felt severe pain in the region of the heart and became faint, and in the evening his breathing became difficult. These symptoms subsided in a few days, but never entirely ceased. He afterwards got worse till the time at which he was admitted into the hospital. He then had marked symptoms of cardiac disease, a double murmur was heard over the aortic orifice, the pulse was characteristically regurgitant, and he was dropsical. He died three and a half months after the accident. The heart was found to be greatly enlarged. The left angle of the posterior semilunar segment at the aortic orifice was found to be torn from its attachment, so that it was quite loose and readily admitted of retroversion, allowing free regurgitation.

<sup>10</sup> HEIDENHAIN, L. *Deutsch. Ztschr. f. Chir.* 1895, xli, 286.

tation from the artery into the ventricle

In this category of aortic valvular lesions following direct injury to the chest belong the interesting two cases that are reported below

John O a robust fellow aged 26, had been working as a laborer for some years. One afternoon, while he was supporting with his out-stretched arms a two-ton platform standing on edge on the floor, it fell over toward him. He was thrown supine, the weight of the platform falling against his chest. It was raised and the patient pulled away from under it unconscious, he so remained lying on the floor for about five minutes. When he roused, he felt severe aching pain across the front of the chest and in the epigastrium. He also had difficulty in breathing, but suffered no palpitation, cough, hemoptysis, or dizziness at that time. He was then taken by ambulance to a hospital.

The chest showed no deformities, no evidence of external injury, and no ecchymosis. There was diffuse tenderness over the mid-sternal region, the second and third left ribs, and also over the xiphoid region. No fractures had taken place.

Physical examination three months after the accident showed the heart to be markedly enlarged to the left and right. The left border was 12 cm from the median line, outside the nipple line, the right border was 7 cm from the median line in the second, third, and fourth spaces. The apex beat was heaving in the fifth space below the left nipple. Over the apex and precordium, radiating upward to the aortic area and toward the vessels of the neck, there was a loud blowing systolic murmur replacing in good part the first heart sound. Over the base there was heard a short diastolic blowing murmur. There was present a Corrigan radial pulse and also a visible capillary pulse. Over the femoral artery there was heard the pistol-shot sound of ventricular systole and just preceding this was another systolic sound. There was visible brachial pulsation with evidence of slight brachial and moderate temporal tor-

tuosity. The brachial blood pressure was 140/34, while the popliteal blood pressure was 180 systolic and heard faintly to 250, the diastolic pressure sound was heard at zero. The electrocardiogram showed no ventricular preponderance.



Electrocardiogram three months after direct injury to his chest and heart

Fig 4—John O

Radiographic examination revealed some pulmonary congestion on both sides. The heart was horizontal in position, enlarged to the right and left. The left ventricle was rounded and prominent. The retrocardiac space showed a normal descending aorta. There was no definite evidence of enlargement of the left auricle, as demonstrated by contrast-filling of the esophagus. The findings pointed to enlargement of the left ventricle and right auricle and suggested enlargement of the right ventricle.

The blood Wassermann reaction was *four plus*.

The subsequent progress of the case was very rapid. Pain and distressing pressure across the chest became more and more marked, compelling the patient to sit up almost all day and all night. Frequent attacks of cardiac asthma developed with enlargement of the liver, congestion of the pulmonary bases and progressive edema of the legs. The mild antihistaminic treatment that was instituted was not of much help. From the observation of the patient's condition, the sudden death which occurred about a half month after the accident, undoubtedly was not unexpected.

*Summary*—From the history of the severity of the injury in the accident, one is compelled to adduce a causal relationship between it and the condition of aortic regurgitation ending in cardiac failure and death. Because of the four plus Wassermann reaction, we cannot be certain in this case that the heart was normal before the accident. A previously diseased valve is more susceptible to traumatic effects than a sound valve.

Alfred B., a chauffeur aged 37, was inside a truck, unloading it of bags of coffee. After forcefully pulling by means of a hook at a bag of coffee weighing 150 lb., it was suddenly released, hitting him across the left side of the front of the chest and throwing him back against the side of the truck. For a moment he felt breathless "the blow took the wind away." He rested, standing, for about five minutes, "feeling winded," and felt a slight localized pain along the lower front of the left chest, slight dizziness, and blurring of vision. He did not feel faint or nauseated, and did not cough or expectorate blood. He continued to unload lighter bags, and then went home by subway, and up two flights of stairs slowly, feeling the pain which became slightly more intense, together with frequent blurring of vision and dizziness. On walking upstairs, he felt dyspneic, with increased pain and palpitation. He continued at hard work for the following six days, obtaining some help in unloading. During this time, aching pain below the left breast region was continuous, at times, it became momentarily worse, compelling him to draw the truck over to the curb. The pain and inability to draw a satisfying breath persisted, with dyspnea and palpitation on exertion. At times, he awoke during the night, distressed for breathing for a few minutes. There were no anginal attacks.

Physical examination a year after the accident showed very slight prominence of the precordium. The apex beat was faintly seen, diffusely felt in the fifth space and

at the sixth rib, four inches to the left of the median line. The heart borders indicated considerable enlargement both to the right and left. Over the apex, there was a loud blowing systolic murmur, slightly heard toward the left axilla, and faintly in the left interscapular space. Over the aortic area, this murmur was louder and rougher in character, transmitted upward. The pulmonary second sound was louder than the aortic. The basic sounds were not accentuated. There were tender spots over the second left rib, four inches from the median line, and over the sixth left rib, four inches from the midline. The blood pressure was 142/90.

A teleroentgenogram of the heart and aorta showed definite prominence of the cardiac shadow to the right. The aorta was slightly widened.

*Summary*—The patient had definite involvement of the aortic valve, and also involvement of the mitral flap, both on an atheromatous basis. This condition pre-existed for a long time and was not related to the injury. It is, however, definite that following the blow to the chest, the patient developed immediate symptoms which had not been present prior to the injury, and which persisted for a long time after. We must, therefore, assume that there did not occur some direct effect upon the heart, producing the pain and other symptoms. Usually, in such cases, the physical signs are either absent or very slight.

Cardiac injury, with the presence of ecchymosis in the heart muscle, takes a long time to heal, and healing is expedited by rest and avoidance of physical strain. Of course, symptoms due to aortic atheroma may often develop spontaneously and confuse the later analysis of the case.

The most important clinical characteristic of these cases is the immediate



development of physical signs referable to the valvular lesion. Immediately after the injury, the patient may be dazed or unconscious. Dyspnea, palpitation, and pain are prompt in their development, with weakness, dizziness, and often hemoptysis. The pain may be referred to the epigastrium, sternum submammary region, or between the shoulder blades. In aortic valve injury, the patients sometimes feel a sudden tearing of the tissue in the chest. Sudden momentary faintness and dizziness occur which become worse on exertion. These may be associated with palpitation, cardiac asthma, and extrasystolic arrhythmia. Cyanosis and edema usually develop either promptly or later. A loud, rough musical murmur is audible over the entire precordium and often at a distance of one to three cm from the surface of the chest. In traumatic aortic valvular lesions, the patient is immediately totally disabled from his work. In some cases the patient has continued lighter work for a short time while suffering pain.

Although rupture of the mitral valve or chordae tendineae has been produced experimentally in the cadaver, clinical occurrence of this lesion with survival of the patient is not very common. Neither is it as well substantiated in the literature as cases of aortic lesions. However the mechanism of its occurrence is readily appreciated from the theoretical discussion presented above. This lesion is not produced by indirect injury to the heart, such as occurs when an individual falls from a height landing on his pelvis. Of course if the valve was previously diseased a severe in-

jury may cause additional changes. Direct violence to the anterior chest, however, is a rare cause of a mitral valve rupture. More frequently the clinical effect that must be considered in these forms of accident is the aggravation of a previously existing mitral lesion. To illustrate this, the following case reported by Barie is presented.<sup>9</sup>

A woman 56 years old was able to pursue her occupation as a manageress although she had a well-developed mitral regurgitation. One day at work, she fell eight feet down a stairway, violently striking the region of her left breast against the banister. She lost consciousness and spit some blood ten minutes after the accident. That day she developed sharp precordial pain and a sensation of smothering and palpitation. The heart was enlarged. Edema, orthopnea and cyanosis developed in a month. The pulse became small and irregular. The systolic murmur became rough and prolonged. She soon died with pulmonary congestion. Autopsy showed rupture of four of the chordae tendineae of one of the mitral cusps. In this case, aggravation was produced by rupture of the chordae tendineae and the regurgitation was increased.

It is much less easily to be granted that mitral stenosis and aortic stenosis can arise directly from similar causes. That stenotic lesions of the aortic and mitral valves following direct violence to the chest do occur has been asserted and cases have been reported in the literature. Thus Allbutt reports a case of mitral stenosis in which after close inquiry he confidently attributed the lesion to the kick of a horse (1911).

cardiac area<sup>17</sup> The patient was a young man, aged 18, and the symptoms were some months in declining themselves, yet the causal relationship seemed to him conclusive

The mechanism of this has been a matter of speculation Experimentally, Rosenbach produced rupture of the aortic cusps by means of a sound introduced through the carotid artery<sup>18</sup> He found thrombosis at the site of the lesion He then introduced infectious material which created an endocardial inflammation with stenosis in the region of the injured valve It has been therefore assumed that following injury to a valve, stenosis may be produced by superimposed infection Litten and von Leyden likewise believed that minute hemorrhages or superficial laceration following trauma may be the foci for further endocardial pathology, and that thrombotic vegetation may supervene at these points<sup>19,20</sup>

Reubold and Rose consider the stenosis in such cases produced by extravasations of blood which organize and mechanically distort the cusps<sup>21</sup> The valvulitis of traumatic endocarditis is due to contusion It is not of the character of verrucous affection and differs pathologically from the in-

fectious type of inflammation It must be mentioned that a traumatically injured valve is vulnerable to subsequent rheumatic infection Thus the inflammatory process that develops over the wound in a valve may lead to shrinking or scarring with the adhesion of the valve fragments

The physical signs can furnish us data to indicate whether the mitral or aortic valve is the one affected as a result of the accident But we have no way of ascertaining with surety the exact nature of the lesion We can only repeat with Laennec that the exact type or amount of rupture may only be suspected, it is impossible to determine this from physical signs

The duration of life following traumatic rupture of a valve is very variable Immediate death may occur Temporary recovery may be sufficient to allow for the resumption of light work Even healing may occur Prognosis is better in cases with pre-existing valvular regurgitation as in these, the heart has already undergone compensating hypertrophy

In general, mitral rupture is more often promptly fatal than aortic rupture In aortic cases, life may be prolonged for several months, but the prognosis is always grave Traumatic aortic valvular lesions are graver as to life prognosis than the infectious aortic lesions<sup>22</sup> Laennec asserts that tear of the chordae tendineae is less soon fatal than tear of the valve flap itself<sup>23</sup>

<sup>17</sup>AILBUTT, C Transac Clin Soc, London, 1873, vi, 101

<sup>18</sup>ROSENBACH Arch f Exper Path u Pharmak, 1878, ix, 1

<sup>19</sup>LITTEN Ueber traumatische Endocarditis Centralbl inn Med, 1901, xxii 513

<sup>20</sup>VON LEYDEN Rupture der Aortenklappen Berl klin Wchnschrft 1889, xxvi Idem 1892, xxix

<sup>21</sup>ROSE Deutsch Ztschr f Chir, 1885, xx, 319

<sup>22</sup>FOSTER Med Times and Gazette, 1871, ii, 657

<sup>23</sup>LAENNEC Treatise on Diseases of the Chest and Mediate Auscultation Translated by John Forbes, London, 1834

*Injuries to the Aorta*

Besides injury to the aortic cusp, the wall of the vessel frequently suffers in accidents due to direct violence to the front of the chest. A blow on the chest, a sudden fall or the jar of an accident may cause rupture of the aorta with the formation of a dissecting aneurysm. This has been recognized since the time of Vesalius. Usually, the cases present the symptoms of ordinary saccular aneurysm of the aorta, but in one case recorded by Allbutt there was dilatation of the aorta. In aneurysm of the abdominal aorta trauma is a very common etiological factor. The essential pathology consists of a split of the intima and inner portion of the media, a dissecting aneurysm may follow with healing or with a rupture, a saccular aneurysm may form or the wall of the aorta may rupture completely.

Allbutt reports two cases which instance the formation of traumatic aortic aneurysm.<sup>24</sup>

Mr B was a well made man under forty, whose health was excellent. One day, on endeavoring to arrest a carter the man backed his horse in such a way as to jam B between the cart-tail and a stone wall. He was seized at once with intense pain and breathlessness and soon after undoubted symptoms of aneurysm of the ascending aorta were developed.

Dr Moxon published a very similar case.<sup>25</sup>

<sup>24</sup> Allbutt C. Effects of Overwork and Strain on the Heart and Great Blood Vessels—St George's Hosp Reports 1870 v 23

<sup>25</sup> Moxon. Med Times and Gazette 1870 vol 2 page 95

In another case, aneurysm of the descending aorta was caused by a machinery accident. The patient a well-made and previously healthy man was whirled off his feet by a gearing strap and before the engine could be stopped, his chest was caught between the strap and a wheel and was seriously crushed. He suffered intensely from pain and dyspnea, and soon after symptoms of an aneurysm to the left of the sternum were developed.

In all these cases a sudden and violent compression of the systemic arteries distends the aorta at a time perhaps of cardiac systole—the brittle inner coat gives way the blood gradually distends the elastic coats the vasa nerves are palsied a sac forms more nerves are palsied and vasa vasorum are occluded, so that widespread mischief is thus added to the original injury.

Kemp reported a case of traumatic rupture of the aorta in a patient who was struck on the chest by a portion of a stone flywheel, which had separated while revolving at full speed.<sup>26</sup> He had a large abrasion over the sternum. The post-mortem findings in the thorax were an extravasation of blood into the subcutaneous tissues and underlying the pectoralis major an extravasation of the blood into the anterior mediastinum. The sternum was fractured obliquely from above downward and backward at the level of the third and fourth costal cartilages. The lungs were deeply congested. The pericardium was greatly distended with blood which had escaped from a transverse tear of the

<sup>26</sup> Kemp. Lancet 1872 ii 113

aorta, just beyond the line of the aortic valve. The exuded serum was under considerable pressure.

In McWeeney's cases, the aortic arch and the left pulmonary artery beneath was torn across three-quarters of an inch beyond the left subclavian by a fall from a scaffold.<sup>27</sup>

McFadzean reports the case of an old man who died suddenly one morning when attempting to rise from bed.<sup>28</sup> Necropsy showed the presence of four aneurysms occupying the whole extent of the abdominal aorta and the greater part of the external and common iliac arteries. All the large arteries of the abdomen, from the origin of the celiac axis to the termination of the external iliac arteries on either side, were degenerated, calcified, irregularly dilated and aneurysmal. The patient had been an acrobat, a strong man and trapeze artist. Almost every day, for twenty years, he spent some time swinging and turning on a hard trapeze and rolling round the instrument on his stomach. This may have been a probable cause of the extraordinary aneurysmal condition of those vessels which, in the process of his acrobatics, would be most exposed to injury. There were no postmortem signs of syphilis.

#### *Injury to the Heart Musculature*

A number of cases in the literature indicate strikingly that due directly to external violence, small foci of myocardial damage may develop. Cases

reported by Fisher<sup>29</sup> and Reubold<sup>30</sup> were each concerned with a serious accident, in which severe trauma took place without any penetrating wounds or rib fractures in the region of the heart. At autopsy, the pericardium was found torn and there were only superficial wounds of the myocardium. Death in these cases was due either to concomitant injuries to other parts of the body, or to hemorrhage into the pericardium from the superficial myocardial wounds.

A diagnosis of myocardial injury in such cases, if feasible, is important as surgical measures might be curative. But when other parts of the body are injured simultaneously the diagnosis is exceedingly difficult.

Whenever a colliding force has been directed against the precordial region of a patient, the possibility of myocardial damage must be kept in mind. If fracture of the ribs or injury to the pleura occurred such suspicion becomes emphasized. The presence of irregular action which supervenes upon violence to the heart is a significant sign. Although the pain has no particular characteristics, it is usually localized over the injured area and sometimes radiates to the left axilla or below the left breast. In most cases of myocardial damage due to external violence, the signs of a transitory pericarditis develop. Usually the heart sounds are lessened in volume.

<sup>29</sup>FISCHER Die Wunden des Herzens und Herzbeutels. Von Langenbeck's Arch f klin, Chir 1868, 12, 571

<sup>30</sup>REUBOLD Bemerk über die Quetschungen Friedrich's Blätter f gerichtl Med, 1870, 21, 285

<sup>27</sup>MCWEENEY Brit Med Jour, 1903, 1, 251

<sup>28</sup>McFADZEAN Brit Med Jour, 1928, 11, 154

and deficient in muscular quality, although no murmurs need be present. Particularly significant is the persistence of a rapid heart rate in the absence of fever. The irregularity of the pulse and its variability of rate are very important.

It must emphatically be recognized that milder injuries of the myocardium may take place consistent with life over a varying length of time. The symptoms and signs, as well as the disability in such cases, usually persists.

Direct violence to the chest may, of course, act like a previous disease in pre-disposing the heart of a person to the effects of heart strain. Usually, however, the resulting condition must be attributed to the direct violence rather than to the strain, for the reason that the aggravation of symptoms by effort usually develops within a short time after the violence. Thus, in a case of Schuster's, a healthy laborer, 43 years old, received a blow in the chest by the harness bar of a wagon, and was thrown back to the ground.<sup>21</sup> He immediately recovered, except for some pain which persisted for two weeks. At that time, following a hard strain of lifting, he developed a sudden and severe epigastric pain radiating around to the chest and back, with a choking sensation. The patient threw himself screaming to the ground in extreme anxiety. There was marked epigastric tenderness, but the pulse rate and heart appeared normal. The following day, large doses of morphine pro-

duced some relief, but he was still pale, cold, cyanotic, and the heart action and tone were weak. The pulse was very small and of normal rate. He died suddenly after a few hours. Autopsy showed hemorrhage into the anterior and posterior mediastinum and also into the pericardium. Under the epicardium of the right auricle there were a number of hemorrhages. One of these encircled the coronary artery and vein, encroaching on their circulation. There were also hemorrhages under the endocardium of the right auricle. Extravasations of this kind were also present in the muscular substance of the left ventricle as well as the endo- and epicardium. The aortic wall was torn horizontally just below the semilunar ring. This tear involved the intima and media and a small dissecting aneurysm was present. There was no pathological process of any kind in this region.

In this case, it is amazing that with such extensive injury to the heart muscle and aorta the patient was able to do even strenuous work for a time and felt only moderate pain. The rise in blood pressure, entailed by the additional lifting two weeks after the original accident, apparently produced the severe symptoms and total disability that terminated in his death. In such cases the aggravation produced by strain was secondary. The essential liability falls upon the circulatory injury by violence.

We may include the following interesting case of ours in this group.

Christino G. aged 45, fell from a high truck for two years with a fracture of scapula. On day after the fall

<sup>21</sup>SCHUSTER, *Ztsch. f. Heilkunde* 1880  
1: 417

falling from a height weighted the far end of the hand-truck, catapulting the handle end upward. The cross-bar struck the patient across the sternum, just at the manubrio-gladiolar junction. He took two or three steps back, fell to the ground unconscious for a few moments, and was dazed when he got up. He felt a severe burning pain in the midsternal region, with dyspnea and distress in taking a satisfying breath. The burning was also felt in the mid-dorsal region, but did not radiate to the arms, neck or other points of the chest. There was also dizziness after moving.

One month later, he developed inconstant pain in the left nipple region, for which he stayed in bed for one week. He returned to bed at times with a burning sensation in the middle of the chest, and a sticking pain in the nipple region. He became fatigued easily and had faintness at times after the accident. At times, he also felt a sudden rapid palpitation, especially during the night and slept only spasmodically, waking with pain, burning sensation, dyspnea, and cough. There was no wheezing nor hemoptysis. Gradually the burning sensation lessened and he then felt the sensation of a lump in the midsternal region. At times, he also had pain in the same region on deep breathing. For seven months after the accident, he could not lie on either side and later could not lie on the left side.

Physical examination a year and a half later showed the heart not enlarged and the sounds at the apex of good quality. Over

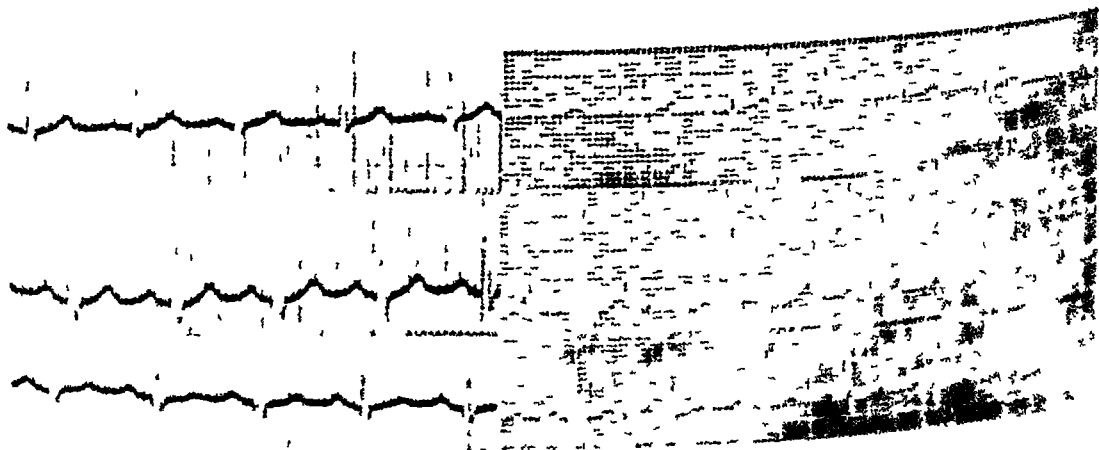
the aortic area, there was a soft blowing systolic murmur, but no basic accentuations. There was a tender spot on the third left rib, two inches from the median line, and also tenderness over the sternum just below the manubrio-gladiolar junction. The temporals were tortuous, and the blood pressure was 132/90.

A teleroentgenogram showed the cardiac shadow normal in size and configuration but the aorta appeared moderately elongated with slight prominence of the descending portion of the arch.

One year later, the patient developed angina pectoris with repeated typical attacks of pain in the precordial and sternal regions, radiating to the left arm. There was weakness and inability to move about with comfort. Examination showed a pulse rate that increased considerably on slight exertion, and a low blood pressure. Otherwise the physical examination showed no new evidences. The electrocardiogram which had previously been negative, at this time showed a conspicuous alternation of the R wave. Otherwise, the waves would be considered entirely normal.

The disability was adjudged total and permanent.

*Summary*—The clinical sequence of events is definite. Following direct injury to the chest wall, the patient became unconscious. The subsequent symptoms that followed are the main



guide and evidence of some affection behind the sternum. Involvement of the aorta or heart, and even laceration or contusion with ecchymosis may occur following severe injury. Over the aortic area, there was a soft systolic blowing murmur. There was a tender spot on the third rib, two inches from the midline as well as below the manubrio-gladiolar junction. Thus, together with the x-ray findings, indicates aortic involvement. There is evidence of slight general arterial changes, which are no doubt of the same type as the aortic lesion and entirely independent of the injury. The later development of angina pectoris is corroborative evidence of the localization of the traumatic lesion. The atheromata in the aorta following the injury obviously spread to the coronary arteries and induced the attacks of angina pectoris.

It is mainly, however, by the record of the injury and the patient's symptoms that we are compelled to conclude that there was damage to the aorta with subsequent cardiac symptoms and angina pectoris all on the basis of the accidental lesion. There may also have been injury to the connective tissue at the base of the heart in the region of the insertion of the large vessels into their pericardial covering. This is speculative, however. The duration of the symptoms is usually much prolonged. It often takes years before the patient can resume strenuous activity and the pain often recurs.

The case reported by Joachim and Mays was that of a man aged 25 who had no history, signs or serologic evidence of syphilis and no valvular

lesions, coronary disease, or diffuse myocardial changes.<sup>32</sup> There was evidence of interstitial myocarditis near the site of the aneurysm. The aneurysm was not located at or near the apex. The only discoverable etiologic factor was an injury to the chest at the age of 12 when he was run over by a wagon and sustained a fracture of some ribs on the left side. At the age of 23 he began to have severe attacks of paroxysmal tachycardia with a heart rate of 170-200. These attacks lasted from ten minutes to as long as one week. There was cyanosis, slight enlargement of the liver and congestion of the bases of the lungs in the severe attacks. He died suddenly. Autopsy showed an aneurysm of the anterior wall of the left ventricle, not near the apex, and composed largely of lime salts. There was also marked interstitial myocarditis and atrophy of the muscle fibres in the surrounding region.

#### RUPTURE OF THE HEART

The relation of trauma to rupture of the heart is well recognized particularly when it concerns penetrating wounds. Traumatic rupture is generally due either to gunshot wounds or to stab wounds. These will be taken up at the end of this section. We shall here concern ourselves with rupture of the heart due to a non-penetrating injuries. This may follow a blow, a fall or a compression injury to the chest as well as violent exertion some time after the injury has been received. It was first described by

far as we can learn, by William Harvey<sup>33</sup>

Morgagni, who himself died from it, described it in an old woman of 75, who had the traditional fatty heart<sup>34</sup>

The symptoms of rupture of the heart are in reality the terminal phenomena that take place. They usually consist of the momentary symptoms of collapse and sudden death.

In the few cases where examination of the heart was made just preceding death, its action was rapid and tumultuous, often irregular, and the sounds of poor quality. A continuous muffled, low-pitched, rushing rumbling has been described as indicating the pouring out of blood into the pericardial sac<sup>35</sup>. The mechanism for the occurrence of death depends upon the intrapericardial pressure<sup>36</sup>. When the pressure in the pericardium becomes equal to that in the right auricle, blood no longer enters the heart from the systemic veins and death promptly ensues.

Traumatic rupture of the heart within an intact pericardium is almost certainly due to compression or concussion. Either of these accidents may directly injure the heart tissue by bruising from without, or else may so raise the intracardiac blood pressure

that the healthy heart wall is burst from within. Compression will vary with the amount of colliding force, while concussion will depend on the rapidity of its application. The site of rupture of the heart in traumatic cases is more frequently in the right ventricle than in the left on account of its closer proximity to the anterior chest wall.

Krumbhaar and Crowell report a very interesting case with autopsy findings, showing a very pointed relation of the trauma to rupture of the heart<sup>37</sup>. A man, aged 38, of dissolute habits, during a drunken debauch at Atlantic City, fell heavily against a box for mixing mortar, hitting the edge against his precordial area. When seen several days later, he had considerable precordial pain, but no diagnosis was made. No further details were available except that death occurred suddenly. At autopsy, the pericardial cavity was filled with clot of blood. About half way up the outer wall of the left ventricle in the visceral pericardium, was a transverse tear, 3 cm in length which extended into the myocardium for about two-thirds of its depth. Histologically, the coronary arterioles were reported as occluded, and the myocardium near the rupture was acutely necrotic.

It is probable in this case that trauma played a prominent part, by injuring the coronary artery with subsequent thrombus formation. Rupture occurred "spontaneously" as a result of the thrombosis.

<sup>33</sup>HARVEY, WM. Works Translated by Sydenham Soc. 1847. P. 127.

<sup>34</sup>MORGAGNI. De Sedibus, Venice, 1761, Epist. 58. No. 14.

<sup>35</sup>REZNIORF. Jour. A. M. A., 1922, LXXXIII, 1926.

<sup>36</sup>HOPKINS. Proc. N. Y. Path. Soc., 1910-1911 (NEW SERIES), 2, 209.

<sup>37</sup>FRANCOIS-LEANCE. Gaz. Hebdomad. 1877, 218.

<sup>38</sup>KRUMSHAAR AND CROWELL. Jour. Med. Sci., 1925, clxx, 82.



The following group of cases also present the typical picture of this type of case

Kennedy reports the case of an emaciated woman of 60 years who was struck in the chest by the shaft of a cart and died in an hour<sup>38</sup> No external bruising was present The second, third, fourth and sixth ribs of the right side were fractured The pericardium however, was untorn and healthy and the heart muscle showed some brown atrophy In the anterior wall of the left ventricle there were two ruptures on a level with the transverse fracture of the sternum There were also some patches of hemorrhage under the epicardium, and also hemorrhage in the tissues around the origin of the great vessels The pericardial sac was filled with blood There can be little doubt that the blow on the chest was delivered with considerable violence, yet there was no bruising visible externally The rupture occurred by bursting, due to concussion

O'Neill records the case of a boy who fell down and was stamped on<sup>39</sup> He was kept in bed for two days and was then allowed up in the absence of severe symptoms He was apparently well for four days and died suddenly in bed the following day Autopsy revealed a hemopericardium and a slit 3 mm long above the auriculo-ventricular ring

Turner and Gould report the case of a boatswain aged 47 who fell forward off his ship a distance of 20

feet on to a buoy<sup>40</sup> He was unconscious when picked up, but no external injuries were found An hour and a half after the accident, he was unconscious, moving his limbs, and shouting in a state of cerebral irritation He became conscious several hours later, but the heart sounds were distant and feeble, and the radial pulse impalpable There was no bruising of the chest wall He died suddenly five hours after the accident There was a fracture of the first segment of the gladiolus The periosteum of the deeper surface was torn by the jagged edge of the fracture The pericardium was filled with blood and there was a small tear in the anterior wall of the right ventricle close to the semilunar valves There was a small bruise, but no tear of the parietal pericardium immediately in front of this

Bilderbeck records the case of a young man aged 19 who was crushed between a stone wall and a wheeled fire-pump as it rolled downhill<sup>41</sup> The cross bar handle caught him across the middle of the chest He was seen to fall dead at once The ribs were unfractured There was no trace of old disease in the heart muscle or its valves In the wall of the right auricle there was a small rupture The pericardium was full of blood, but undamaged The explanation is that at the moment of impact the man may have taken a deep inspiration engorging the right auricle which then burst on sudden compression through the costal wall

<sup>38</sup>TURNER AND GOULD, *Lancet* 1917

<sup>39</sup>67  
<sup>40</sup>BILDERBECK, A. C. I. B. & M. J. R. 1910 175

<sup>38</sup>KENNEDY, *Lancet*, 1914, 1 105

<sup>39</sup>O'NEILL, *Jour Am Assoc* 1914, 21

Howatt reports a case of traumatic rupture of the heart in an adult male, aged 23. The man fell 45 feet, alighting on a wooden plank and a pile of steel plates.<sup>42</sup> The death was not instantaneous, the patient dying twenty minutes after the accident, in a hospital. Externally there were practically no evidences of injury. Autopsy revealed that the pericardium was distended with blood, due to a rupture of the free edge of the left auricular appendage.

In this case, the injuries were caused by the violent impact of the body against the ground. The nature of the cardiac rupture raises the question as to the mode of its production. Trauma may cause injury of the heart's wall without immediate rupture, but after an interval the injured area may prove the site of a rupture, which may be described as "delayed traumatic" or "spontaneous" according to predilection. Where the interval between the receipt of the injury and death is considerable, difficult questions about the cause of death may be raised by claims for monetary compensation or damages.

Howatt also records a case in a bricklayer aged 68 who was squeezed between a wall and a small passing truck which scraped the skin on the front of his chest, doing no further apparent local injury. He was in bed for two weeks and resumed work after three weeks, in apparent good health, and with normal pulse rate. After three days of work, he felt disabled by pain in the chest and re-

mained abed. His pulse rate rose gradually and after two weeks of rest, he suddenly died. The heart muscle and the pericardium were not the seat of any disease. The left ventricle was bruised in five places, the largest bruise, in front near the apex, extending through the greater part of the wall's thickness. Here the ventricular wall was ruptured and the pericardial sac was filled with blood.

Howatt also reports three other cases of traumatic rupture with intact pericardium. One resulted from a shell wound of the skin in the left mid-axillary line with comminuted fracture of the fourth and fifth ribs. The anterior wall of the left ventricle showed a vertical perforation. The pericardium was intact. Such an injury points to contusion of the heart wall by the broken ribs acting through the pericardium, and concussion from the violence of the trauma.

In another gun-shot case, there was a non-penetrating wound of the thoracic wall, without fracture. The anterior wall of the right ventricle showed a minute rupture and the pericardium was distended with blood.

Spontaneous rupture of the heart may bear a definite, although somewhat delayed relationship to direct injury to the chest. This is illustrated by the case of Krumbhaar and Crowell above recorded, and the following three cases in which death took place at some time after injury, where no immediate effort or trauma seemed to play any part. Two are by Dreack, one, a workman of 58, who nine months before his sudden death had been struck twice on the chest and

<sup>42</sup>Howatt, R. K. *Lancet*, London, 1920, i, 1313.

visibly bruised<sup>43</sup> Subsequently he continually complained of pain in the chest Fourteen days before death, he developed influenza, and at autopsy was found to have a rupture of the apex in an aneurysm which had developed subsequent to the injury It was therefore considered that it was a "spontaneous" rupture with trauma as the underlying cause

The second was a girl of nine who had fallen down stairs five weeks before death, which occurred suddenly on getting out of bed The rupture in the right ventricle was thought to be dependent on the former trauma The muscle was said to be normal The third case is reported by Corn and concerns a miner of 62 who, fourteen days before his sudden death had been crushed by a wagonload of coal, but did not stop work at the time<sup>44</sup> There was no external lesion or bruise of the thoracic muscles or bones at autopsy and the author thought that the rupture of the left ventricle should be traceable to the history of traumatic injury to the heart

In the etiology of those cases in which spontaneous rupture takes place following exertion, coronary sclerosis holds a pre-eminent place In consequence, there develops ischemic necrosis with thinning and replacement fibrosis and the formation of aneurysm of the left ventricle due to the high intraventricular pressure Fatty

infiltration of the heart muscle or brown atrophy due to the slow coronary sclerosis of age may exist In all these cases, the sudden increase of blood pressure during work plays a critical role in precipitating the rupture of the heart

From experiments on animals it seems that on suddenly produced insufficiency of the aortic valve, the intraventricular pressure may become so great as even to rupture the unprepared ventricle In one such case reported, there occurred also sudden rupture of the posterior pillar of the lower mitral cusp<sup>45</sup> It is almost certain, as was maintained by Morgagni, that a complete rupture never occurs through the sound heart muscle

#### PENETRATING WOUNDS

Besides rupture and laceration of the organ produced by contusions and crushing injuries, external penetrating wounds of the heart occur, passing through one or more of the heart walls Gunshot wounds constitute a large percentage of the penetrating wounds of the chest In addition to these fractures of the ribs and sternum play an important role In these cases, the sharp end of a broken fragment may directly lacerate the tissues of the heart The seriousness of these injuries depends upon the amount of trauma inflicted upon the intrathoracic structures<sup>46</sup>

Penetrating wounds of the thorax

<sup>43</sup>DREACK Giessen Dissertation, 1900 This and a number of other references to the subject were kindly supplied by Dr E B Krumbhaar of Philadelphia, to whom we are deeply grateful

<sup>44</sup>CORN, M G Bull de l'Acad Roy de Med de Belg 1911 xx, 563

<sup>45</sup>BOURRIAN, quoted by Alphonse Savignol, *System of Medicine* 1909 Vol 1 p 425 MacMillan & Co London

<sup>46</sup>KELLS *Surgical Statistics* Philadelphia 1910 Vol 1

associated with wounds of the pericardium or heart are always accompanied by severe shock. When the great vessels are involved, death generally follows in a few moments. These conditions must always be considered serious and naturally treated as emergencies.

The usual site of the penetration is one or the other of the right chambers of the heart, as the wound is generally received from in front. The wound in the pericardium permits of escape of blood, and thus lessens the risk of fatal embarrassment of the heart's action by the increased intrapericardial pressure due to hemopericardium.

The prognosis in penetrating wounds of the chest is always serious. Yet, a number of cases have been amenable to immediate repair with subsequent recovery. In these cases, certain post-traumatic disturbances of the heart may result. Adhesive pericarditis may develop after recovery. If there is lodgement of the foreign body in the myocardium, removal will result in a localized lesion which may be the focus for extrasystoles.

Freese reports a case of a negro who was stabbed and immediately operated on while he was unconscious, with feeble respirations, imperceptible pulse, widely dilated pupils, and cold perspiration.<sup>47</sup> There was a wound half an inch long, in the fourth space to the left of the sternum. After removal of part of the fourth and fifth left ribs and the costal cartilages, a wound of the pericardium was seen exuding blood. When the clot was

removed from the pericardial sac, the heart wound was seen in the posterior wall of the left ventricle, a little above the apex. This was sutured, the pericardial wound closed, and the musculo-cutaneous flaps replaced on the chest wall. The patient recovered without any subsequent cardiac embarrassment.

Under this heading belongs also the consideration of the question of injuries to the blood vessels and thoracic wall. These frequently complicate penetrating wounds. The internal mammary artery and intercostal arteries may give dangerous and even fatal hemorrhages within the chest. The rupture of the larger vessels in the thorax such as the superior vena cava has also been discovered following penetrating wounds.

In one case, reported by Stephens, a man of 42 fell into a cellar, fracturing the sternum at the sternal angle.<sup>48</sup> On opening the chest, a marked extravasation of blood was found behind the site of the fracture, due to a tear in the superior vena cava.

There is a case reported by Fisher of a negro 24 years old who was stabbed just within the left nipple.<sup>49</sup> He was in extreme shock with cold skin and barely palpable pulse. Under ether anesthesia, blood was found to escape from a wound in the pericardium and an attack of paroxysmal ventricular tachycardia was observed. There was also a penetrating wound

<sup>47</sup>FREESE Jour A M A, 1921, lxxvi, 520

<sup>48</sup>STEPHENS Lancet, London 1922, ii, 1382

<sup>49</sup>FISHER, J L The Repaired Heart Jour A M A, 1926, lxxvi, 192

over the left ventricle, one inch long which was grasped and sutured. The patient recovered.

There are recorded in the literature several such interesting cases. Some of them are of stab wounds which required suture and resulted in complete recovery.

#### COMPENSATION CRITERIA

In considering the subject of trauma to the thorax with intrathoracic cardiovascular injury from the point of view of the compensability of the accident several important criteria must be established.

1 From a labor standpoint, the heart is healthy if a man is able for a long period of time to pursue his occupation without distress and without long periods of absence from work.

2 If following direct or indirect violence to the chest signs of an intrathoracic cardiovascular lesion develop which are incapacitating they must be considered the result of an aggravation of a previously-existing asymptomatic lesion, or the result of damage to a previously normal heart.

3 As in heart strain, the time that elapses between the accident and the development of disabling symptoms is very short. There must be immediate pain with its concomitants—dyspnea, rapid irregular pulse, faintness, and cold sweat, and immediate partial or total disability in order that causal or aggravating relationship be clearly established. Temporary improvement with return to usual or lighter work followed by a recurrence of the condition may occur. But in these cases

the re-appearance of the symptoms and signs should be attributed to the original injury.

#### SUMMARY

1 The superficial position of the heart and pericardium directly behind the sternum and the adjacent cartilages exposes it to danger from injuries to the anterior chest wall.

2 With or without injury to the ribs, or even without obvious external bruising, an external blow may produce very serious damage to the intrathoracic structures.

3 The principal clinical types of traumatic heart lesions that occur in consequence of direct and indirect violence are classified.

4 The pericardium may react to a contusion or concussion of the chest with the development of acute pericarditis.

5 Atrial fibrillation may follow direct violence to the chest. Illustrative cases are reported by the authors.

6 Extrasystolic arrhythmia may arise following damage produced in the cardiac tissue by direct injury to the organ from blunt violence such as blows to the chest or indirect injury as in falling from a height.

7 The location of the trauma in the myocardial structure will predicate the functional disturbances or arrhythmia that may develop. Cases are reported of heart block from direct injury to the chest.

8 Injury to the front of the chest with or without injury to the ribs or even without obvious external bruising may cause rupture or closure of the valves of the heart.

9 The mechanism of the production of such injuries is discussed

10 The most important clinical characteristic of these cases is the immediate development of physical signs referable to the valvular lesion

11 Besides injury to the aortic cusp, the wall of the vessel frequently suffers in accidents due to direct violence to the front of the chest, with the formation of a dissecting aneurysm

12 A pre-existing aneurysm may rupture in consequence of direct blunt violence to the thorax

13 A number of cases in the literature indicate strikingly that due directly to external non-penetrating violence, small foci of myocardial damage may develop

14 It must be recognized that milder injuries of the myocardium may take place consistent with life over a varying length of time

15 Rupture of the heart may follow non-penetrating injuries to the chest, as well as violent effort, some time after the injury has been received

16 The symptoms of rupture of the heart are in reality the terminal phenomena that take place. They usually consist of the momentary symptoms of collapse and sudden death

17 The mechanism for the occurrence of death depends upon the intrapericardial pressure. When the pressure in the pericardium becomes equal to that in the right auricle, blood no longer enters the heart from the systemic veins and death promptly ensues

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<sup>5</sup>KNOCKER, D. Accidents in their Medical and Legal Aspects. Bailliere, Tindall and Cox. London, 1910. Page 240

<sup>6</sup>MARKOFF, N. Über die Traumatische Entstehung der Herzklappenfehler. Diss. Zurich 1902

# On Measurements of the Renal Veins: A Contribution to the Literature of Postural Albuminuria

By CLARENCE QUINAN, M D , *San Francisco, California*

IT may be affirmed as literally true that our knowledge concerning the mode of origin of the so-called physiological albuminurias is not much greater now than it was forty years ago. Indeed in the somewhat extensive literature that deals with these functional disorders there is only one necropsy report to be found and according to that report (1) the examination was negative in its results except that a small and apparently insignificant lesion was found in one kidney. It would therefore seem justifiable to bring forward objective data of almost any description, if only they enable us to make progress toward the discovery of a causative mechanism. In pursuance of this idea, I describe here very briefly various clinical and other data noted down from year to year during the study of what seems to have been a remarkable, if not a unique, case of postural albuminuria. The patient, a young man who had had a severe form of this disorder since childhood, finally succumbed to an attack of broncho-pneumonia. The renal vein measurements recorded in this paper were made in consequence of certain unusual facts observed during the post-mortem examination.

As I have already published an account of this patient's clinical history, (2) for the present purpose it will suffice to outline the main features of his case.

## REPORT OF CASE

*History*—T. T., a man, aged 23, seen first, Jan. 20, 1915, who appeared to be in good health and whose family history was unimportant, stated that in his seventh year following an attack of whooping cough albumin was discovered in his urine. It had persisted ever since. Apparently, however, the trouble had not affected his health very materially, since for a number of years he had led an active out-of-doors life as a "field-naturalist."

*Examination*—The patient was well developed, muscular, and his figure was erect, athletic and showed no trace of lordosis. His height was 5 feet 8 inches (174 cm.) and he weighed 148 pounds (67 kg.). With the exception of a slight facial pallor, he looked physically fit. The right kidney was freely movable, the left could not be felt. In other respects, the examination of his trunk and extremities was negative in its results. The eye grounds were normal.

The urine contained a large amount of albumin and a few hyaline casts were found in the sediment. He was instructed to bring for examination samples of his urine collected (1) before rising in the morning and (2) after being up and about for some time. The specific gravity of the first specimen was 1.020 and another voided at the same time was 1.015, respectively. 0.75 Gm. and 7.5 Gm. of albumin were found in the first and second samples, respectively.

It was not until May 4, 1922, seven years later, that I was enabled to resume the study of this patient's case

His life during this intervening period had been an extremely active one For he had served throughout the war as an officer in the aviation corps of the A E F—he said that he had been enabled to pass the physical examination required in this branch of the military service simply by substituting for his own urine that of a comrade, and, since the war, he had been an outdoor solicitor for a steamship company, a line of work which had kept him almost constantly on his feet

May 4, 1922, his general physical status remained much the same as it had been in January, 1915 His blood pressure was 122 systolic, 85 diastolic, and it was not appreciably modified by change of posture The eye grounds were normal The albuminuria persisted

As it seemed possible that the massive output of albumin characteristic of all urine specimens voided by this patient when he stood erect might be related in some way to the fact that his right kidney was freely movable, numerous experiments were made with a specially devised apparatus by means of which the kidneys, either singly or both together, could be quite securely held in place Without exception, however these experiments were negative in their results, for quantitative tests made with specimens of urine collected by this patient while

upright, with the apparatus in place, showed that the albumin output was not in the least influenced by fixation of either one or both of the kidneys On the other hand, it was proved by experiments that his clinostatic albuminuria could be notably reduced in amount through the simple expedient of having him sleep in a bed the foot of which had been raised about six inches

Although the urine of this patient was heavily albuminous at all times, it was characteristic that the maximum output of albumin in the urine occurred only after he had left his bed and had been up and about for some time The average rate of albumin elimination was determined by Esbach's method The tests—120 in all—were made at regular intervals during a period of five months The average values thus obtained were 124 parts per thousand for the specimens collected in the horizontal posture, and 430 and 760, respectively, for the specimens voided while he was on his feet at 7 20 and at 7 40 A M—see Fig 1

That the postural albuminuria was remarkably constant in character can be seen at a glance by comparing the data noted at different times during a period of eight years, see Table 1

TABLE 1—ALBUMIN ELIMINATION DURING A PERIOD OF EIGHT YEARS IN A CASE OF POSTURAL ALBUMINURIA

	Albumin in Parts per Thousand		
	7 00 A M	7 20 A M	7 30 A M
	Patient	Patient	Patient
	Horizontal	Vertical	Vertical
	No 1	No 2	No 3
Jan 20 1915			10
May 4 1922	075		25
Jan 18 1923	225	100	55
	000	375	



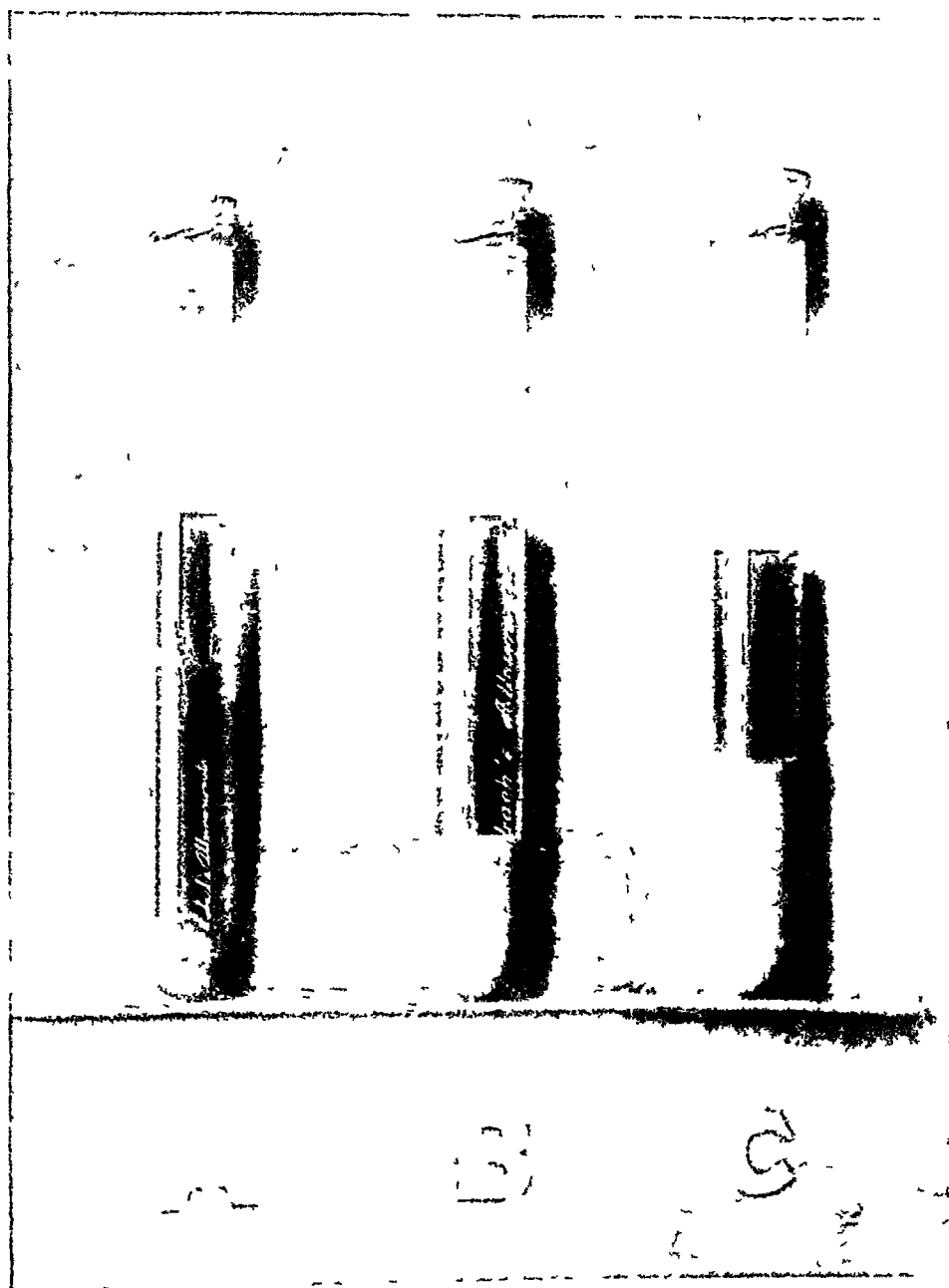


FIG. 1. Typical Ishikawa tests. Appearance after twenty-four hours. A. Vertical specimen, 7 AM, patient recumbent. B. First vertical specimen, 7:20 AM, second vertical specimen, 7:40 AM.

January 28, 1923, in consequence of having been chilled through exposure, he contracted broncho-pneumonia and died after an illness of eight days

The post-mortem examination showed that death had been due to broncho-pneumonia, complicated with acute bilateral pleurisy and acute suppurative pericarditis, but it also disclosed an extremely remarkable condition of visceroptosis, as may be seen from the following report as to the abdominal findings

*Autopsy Report*—The liver projects over a hand's breadth on both sides. The stomach is pushed far down. The fundus is three fingers below the umbilicus. The transverse colon is a little above the symphysis. Most of the small intestine is in the pelvis.

The right kidney is rather loose, and it is distinctly displaced downward. The lower edge of this kidney is just opposite the crest of the iliac bone, on top of the ileo-psoas muscle. The hepatic flexure is fastened in this same region. The transverse colon then runs in a large U-shaped loop down to the symphysis and up along the greater curvature of the stomach to the lower pole of the left kidney which is in its normal position, slightly looser than it should be.

The liver is displaced downward and it is somewhat loose in its attachments posteriorly. It is unusually large, easily one and a third times its normal size. Both lobes are equally enlarged. Its shape is normal. The surface shows passive congestion and edema. The hepatic artery is normal. The liver weighs four pounds (2154 grams).

The two renal veins are both very wide. They arise from the vena cava at the usual level. The left renal vein measures 18 millimeters, the right 16 millimeters in diameter.

The left kidney capsule strips easily. The kidney is smooth and purplish in color. It measures 125 by 55 by 25 millimeters. So, all irregular, ill-defined yellow spots are

visible on the surface. The left kidney weighs 170 grams.

*Cut Surface*—The cortex measures approximately six millimeters. It is rather opaque and slightly yellowish. The columns of Bertini are of the same color. The pyramids show slight passive congestion, otherwise they are normal.

The right kidney capsule strips easily. It is slightly thickened and more whitish than the left. The cut surface is smooth. This kidney measures 102 by 60 by 28 millimeters. It weighs 113 grams.

*Histological Examination*—(a) Liver. The sections show moderate peripheral fatty degeneration. The arteries are normal.

(b) Kidneys. There is fibrosis of many glomeruli, much new fibrous tissue with atrophy of tubules and moderate round celled infiltration, here and there comparatively normal tubules show much granular and some fatty degeneration. Some of the cells seem to be full of crystals of fatty acid, few casts, slight endarteritis of some of the arteries. In places the new connective tissue appears to contain large, irregular granules of calcareous material.

## MEASUREMENTS OF RENAL VEINS

In view of the fact that a marked postural albuminuria had been for many years this patient's only symptom, it was natural to be struck by the circumstance, noted in the autopsy report, that both of his renal veins appeared to be very large, but, of course, no significance could be attached to such a finding unless it could be shown that the vessels mentioned were, in fact, oversized. Since, however, the text-books are virtually silent on the subject of the renal veins and say nothing as to their variations in caliber, in order to determine the average size of these vessels it became necessary to attack this problem at first hand. Accordingly, with the view to obtain such data I have

# Measurements of the Renal Veins

1051

measured the collapsed, empty renal veins in a number of human subjects. The data accumulated in the course of this work are shown in Table 2

quite diversified in character, but it should be stated that cardio-renal disease was perhaps the most common cause of death, and that not a few of the subjects were those of appar-

TABLE 2—RENAL VEIN MEASUREMENTS IN 100 UNSELECTED SUBJECTS

P-M No	Age and Sex	Widths of Veins In mms		P-M No	Age and Sex	Widths of Veins In mms		P-M No	Age and Sex	Widths of Veins In mms		P-M No	Age and Sex	Widths of Veins In mms	
		R	L			R	L			R	L			R	L
1	M60	11-10		26	M25	11-12		51	M42	12-12		76	F39	12-10	
2	M60	10-11		27	M42	11-10		52	M40	9-10		77	F45	11-12	
3	M58	12-10		28	F31	13-11		53	F68	11-12		78	F50	9-14	
4	F35	11-12		29	M28	11-11		54	M60	9-10		79	F70	11-14	
5	F25	14-11		30	M45	8-13		55	M60	10-12		80	M60	14-12	
6	M50	12-13		31	M60	10-11		56	M55	11-13		81	M50	10-12	
7	M35	10-11		32	M60	10-14		57	M35	11-10		82	M75	13-10	
8	M34	9-9		33	M45	8-14		58	M41	11-10		83	M40	12-10	
9	M45	8-14		34	F71	11-9		59	M39	10-15		84	M45	8-11	
10	M52	11-13		35	F54	9-10		60	M72	12-11		85	M20	9-12	
11	F35	9-10		36	M40	11-7		61	M36	9-11		86	M38	11-12	
12	M25	12-7		37	M27	14-13		62	M40	11-12		87	M60	10-10	
13	M50	11-11		38	M75	9-11		63	F42	10-13		88	F29	14-12	
14	M30	14-13		39	M55	14-13		64	M40	11-13		89	M55	10-11	
15	M70	15-11		40	M40	9-11		65	F26	12-16		90	F14	10-11	
16	M45	11-10		41	M19	10-10		66	M34	10-14		91	M35	12-13	
17	F45	10-11		42	F30	13-11		67	M45	10-10		92	M40	9-11	
18	M22	10-11		43	F28	12-11		68	M32	8-10		93	F25	13-11	
19	M72	10-12		44	M50	12-9		69	M55	11-12		94	M25	12-14	
20	F45	10-12		45	M70	9-15		70	M45	10-11		95	F42	12-13	
21	F82	9-8		46	M60	12-11		71	F40	12-12		96	M45	10-13	
22	M40	11-13		47	F60	9-13		72	F21	9-10		97	M45	7-11	
23	M55	12-10		48	M17	16-10		73	M50	11-10		98	M60	12-11	
24	M36	13-12		49	M40	10-14		74	M60	10-11		99	M45	9-13	
25	F60	13-11		50	M55			75	F34			100	F40	8-11	

Mean values in mms Right vein 10.7 left vein 11.4

The subjects examined were unselected, except that those only were turned to account whose renal veins were represented by the usual single straight trunks. As the work reported here was done largely in the San Francisco city morgue, it will be understood that from the standpoint of pathology the material employed was

meters as the average total cross-section of these veins

However, besides yielding these average values, the data brought together in this paper, though comparatively few in number, also justify three other seemingly definite conclusions. These are 1 That there is no fixed rule as to the relative widths of the two renal veins. In the present series, for example, the left vein was larger than the right in 57 subjects, in 34 subjects the right vein was larger than the left, while in 9 both veins were of the same caliber. 2 That the total venous path of the kidneys, as shown by the combined diameters of the renal veins, varies within comparatively narrow limits. In a majority of the subjects that I examined it ranged from 19 to 26 millimeters, and since in but a single instance was a value of 28 millimeters noted, it seems probable that values in excess of this figure are probably to be regarded as exceptional. 3 That the total venous path sustains no relation to the total mass of the two kidneys. As a matter of fact, having made careful measurements of each of the two-hundred kidneys used in this series, I can state that as a rule the largest veins occurred in kidneys of medium size whereas, not infrequently, kidneys of relatively huge dimensions had very small veins.

Now, according to the autopsy report, the right and left renal veins of the patient T. T., measured, respectively, 16 and 18 millimeters. In this instance therefore the blood vessels mentioned had a total cross-section of 34 millimeters. However, on comparing these values with those

recorded in Table 2, it becomes evident, not only that each one of the renal veins was unusually large, but that the figure which represents their combined diameters exceeds by more than fifty per cent the corresponding average value obtained in the present study of 100 unselected subjects.

#### COMMENT

Here, then, we have to do with the case of a young man of superb physique, who undoubtedly suffered from chronic nephritis, but whose major and almost only symptom had been for many years a massive albuminuria always exaggerated by the change from the horizontal to the vertical posture. As to the cause of this the main presenting symptom, needless to say, it is only possible to indulge in conjectures that seem to be in keeping with observed facts. Having in mind, however, that the post-mortem examination disclosed a huge liver, loose in its posterior attachments, together with a general downward displacement of other abdominal organs—to say nothing of the greatly enlarged renal veins—I am disposed to believe that in this particular instance both the postural albuminuria and the widening of these veins may have been the end of results of a constantly recurring passive congestion. This, I believe, may have been caused by a partial constriction of the vena cava, probably at the point where it penetrates the diaphragm—that is to say, at the foramen quadratum. As to the nature of the constricting force, I venture to affirm that it may have arisen through a traction-tug exerted upon this great blood vessel by the pro-

lapsed abdominal organs. In other words, I believe that the postural albuminuria was indirectly due to the visceroptosis.

### CONCLUSIONS

1 The average values obtained for the widths of the renal veins, as determined by measurements of these blood vessels in 100 unselected human subjects, were 10.7 millimeters for the right vein and 11.4 millimeters for the left.

2 The average total cross-section value for these vessels was found to be 22.1 millimeters.

3 Exceptionally, one or other of the renal veins may reach a diameter of 16 millimeters, but it is rare for the combined diameters of these vessels to measure over 27 millimeters.

4 Details are given as to the clinical history and the post-mortem findings in a remarkable case of postural albuminuria.

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# Massive Atelectasis\*

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THE subject for discussion this afternoon is a very brief resumé of so-called massive collapse of the lungs with the addition of case reports of two interesting unpublished cases

"Massive Collapse" was first described by the Englishman, W Pasteur, in the year 1890 after study of 7 autopsy cases which presented post diphtheritic paralysis of the diaphragm, the result of nasal and pharyngeal diphtheria. It was not observed in laryngeal cases. The same author twenty years later, in 1910, described "post operative massive collapse" in a study of 2,000 operations in which there was an incidence of 201 post operative pulmonary complications, of which pulmonary complications, 16 or 8% were in the nature of massive collapse. These operations were mostly abdominal sections, chiefly for appendicitis, and herniotomies. No case was observed following operations on the head and upper extremities.

Sir John Rose-Bradford—1918-1920—discovered in a study of war wounds of the chest, whether penetrating or non-penetrating, that 5% to 10% of these were succeeded by the development of more or less massive collapse, but found no evidence of

bronchial obstruction, pleural effusion or any other lesion interfering with the aeration of the lung.

Scrimger in 1921 was the first American to report on the condition, recording seven cases. Within the past seven years the literature on the subject, particularly of that form known as post operative massive collapse, has grown quite rapidly, although conclusive evidence as to the true cause of the condition has never been developed.

It is unfortunate that the early writers have given it the name "Massive Collapse" for it is in no sense of the word a true collapse. The condition is one of airlessness of the lung—atelectasis—usually developing with spectacular acuteness, particularly in the post operative and chest wound cases, though developing not infrequently in a more chronic manner. I shall show in my second case.

Quite an interesting and puzzling feature of the cases following thoracic wounds (and it may follow with such dramatic suddenness that the possibility of infection being the etiological factor can be ruled out by the absence of demonstrable infection and the very suddenness of its onset) is that the condition may be homolateral, contralateral, or bilateral. Nor is the condition always massive but not

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infrequently may be only lobar or even lobular in extent. That no true collapse of the lung exists is well shown by the fact that there is present a markedly accentuated *negative* intrapleural pressure (too high to be recorded by the ordinary water or mercury manometer of the usual artificial pneumothorax apparatus) in contradistinction to the positive pressure accompanying a true collapse. Nor has it been conclusively proven that bronchial obstruction is present though the most recent studies of W. E. Lee and Chevalier Jackson would suggest such a possibility.

The picture of the acutely developed case is briefly a patient who (say, for illustration, has from one to four days previously had an abdominal operation) has apparently a normal set of lungs and bronchi, suddenly without evidence of infection, respiratory or otherwise, and without other demonstrable evidence of serious or impending complications in the midst of a normal post operative convalescence becomes acutely ill with some form of rather malignant pulmonary mischief. Pain may be present or absent, but there is quite marked cyanosis without evidence of previous cardiac impairment, though tachycardia is common and prominent. Dyspnea is usually quite a definite feature depending for its extent largely upon the degree of the atelectasis. A cough develops which is at first non-productive though later there is mucoid and still later muco-purulent sputum—never the bloody or prune juice expectoration of pneumonia—an important point in the differential diagnosis. Chills have occasionally been reported

the rule being for the development of temperature up to say 102 F or 103 F. The white blood cell count usually runs up to about 20,000. The patient is seen to be suddenly acutely ill, and uncomfortable though it is not always that the attention is immediately drawn to the respiratory tract.

In the well developed case the physical findings show a cyanotic, dyspneic patient with marked immobility of the affected side of the chest and narrowing of the interspaces on this side. Vocal fremitus, at first increased, as the condition develops, becomes diminished and then absent with the complete airlessness of the lung. There is dullness to flatness over the affected area, simulating massive fluid, possibly hyperresonance over the rest of the chest and the further absence of all true vesicular breath sounds (only tubular or transmitted tracheal breathing being heard) may cause a similar confusion. Complete absence of adventitious sounds is found and is most important. There is a high immobile diaphragm and the most characteristic finding of all is the retraction of the heart and quite frequently the trachea to the affected side. This of course, is in marked contrast to fluid which naturally pushes the heart and mediastinum away from it. The fluoroscope and stereoscopic films con-

quite readily see then, that you must differentiate the condition from pneumonia, acute dilatation of the heart, pulmonary embolus and infarct, pleurisy, with and without effusion, pneumothorax, and diaphragmatic hernia.

### INCIDENCE

The condition may occur—

- (1) Congenitally
- (2) Spontaneously in the course of diaphragmatic pleurisy—and in the new born without demonstrable defect or disease, as I shall show in my first case
- (3) In infections of the lungs and bronchi, such as pneumonia, purulent bronchitis and tuberculosis (usually chronic)
- (4) With post-diphtheritic diaphragmatic paralysis (Pasteur)
- (5) Post-operatively and following chest wounds, penetrating and non-penetrating
- (6) Due to bronchial obstruction by tuberculosis, neoplasms (my second case) foreign bodies, mucous secretions, etc

Unfortunately time forbids a discussion of the interesting speculation as to its cause

### THE FIRST CASE

(Service Dr J LaB Ward, Biltmore Hospital)

*M E H* Female infant, born March 6, 1927 Normal delivery and child appeared normal in all respects No anomalies or birth injuries

*Chest*—Equal expansion on both sides and breath sounds good Apparently a perfectly normal baby until the beginning of the fourth day at which time she became acutely

ill There was rise of temperature, rapid pulse, dyspnea, cyanosis, temperature to 102 F with the entire left chest, anteriorly and posteriorly, flat to percussion with very distant breathing and no rales heard A little patch, thought to be a pleuritic rub to the left of the nipple Right lung-hyper-resonant

*Blood*—Hbg—95% R B C—4,800,000 W B C 22500 Differential—Neut—56% S L—29% L M 15%

*X-Ray*—Pictures made as shown (Fig 1) and because of the insistence of one of the consultants and the roentgenologist that fluid was present an exploratory tapping was attempted with negative results Neither the pediatrician nor roentgenologist who insisted on exploratory needling, however, was able to offer any convincing theory as to how such massive fluid could possibly occur in a four day old child, born healthy and possessing an apparently normal heart and lungs

Temperature range was from 99 F to 101 F for three days and then the child completely recovered as shown in the films (Fig 2) made six days later than the onset of the acute illness, with complete clearing of the physical signs in the chest

This undoubtedly is a clear cut case of massive atelectasis of the left lung in an infant four days old who was born perfectly normal and has a family history of no bearing whatever on the case The most probable explanation is that the main bronchus was blocked by a plug of mucus which was coughed up and the lung immediately became aerated again

### SECOND CASE

*W T C*—Male—Commercial Agt R R Office work 42-M Wife and three children living and well One office mate left 2 mos previous to Mr C's illness on account of tuberculosis Otherwise no contact with tuberculosis

*Family*—Childhood and past history of no significance





FIGURE 1 M. C. H., March 10, 1927 Complete homogenous opacity of left lung

*Habits*—Heavy cigarette (30 a day) smoker for 25 years

*P I*—Patient felt perfectly well until June 4 1927, when he developed a dry cough. Physical examination, X-ray examination—(Fig 3) all negative. Five weeks later, cough persisting (July 10, 1927) he had a small pulmonary hemorrhage. Went to bed but three weeks later had two small hemorrhages, then having P M temperature to 99 4/5 F. Some cough and expectoration, though little pus in it. Dyspnea only on exertion. Patient kept in bed another three or four weeks and then sent to Asheville, Sept 29, 1927, with suspected tuberculosis. Patient was spitting a slightly tinged sputum which rapidly cleared, but ran temperature from 98 F to 100 F daily with only slight, if any, amelioration of cough. Eighteen days later patient was strong enough to

come to office for examination at which time the essential details of the examination were as follows

*Physical Examination* — Tall, slender, poorly nourished man of 42. Ht 70" Wt 123 lbs, pale, but not cachectic, anxious and worried. Fingers show some clubbing with considerable curving and linear ridging of the nails.

*Chest*—Long, narrow, thin, with right shoulder droop and marked limitation of expansion of the right side. Vocal fremitus and resonance increased over rt upper lobe, diminished below on this side—absent over lower one-half.

*Heart*—Apex in IV interspace 3" to right of mid sternum. Action—rapid, regular, no murmurs. Blood pressure—90-70. Percussion showed dullness over rt upper lobe.



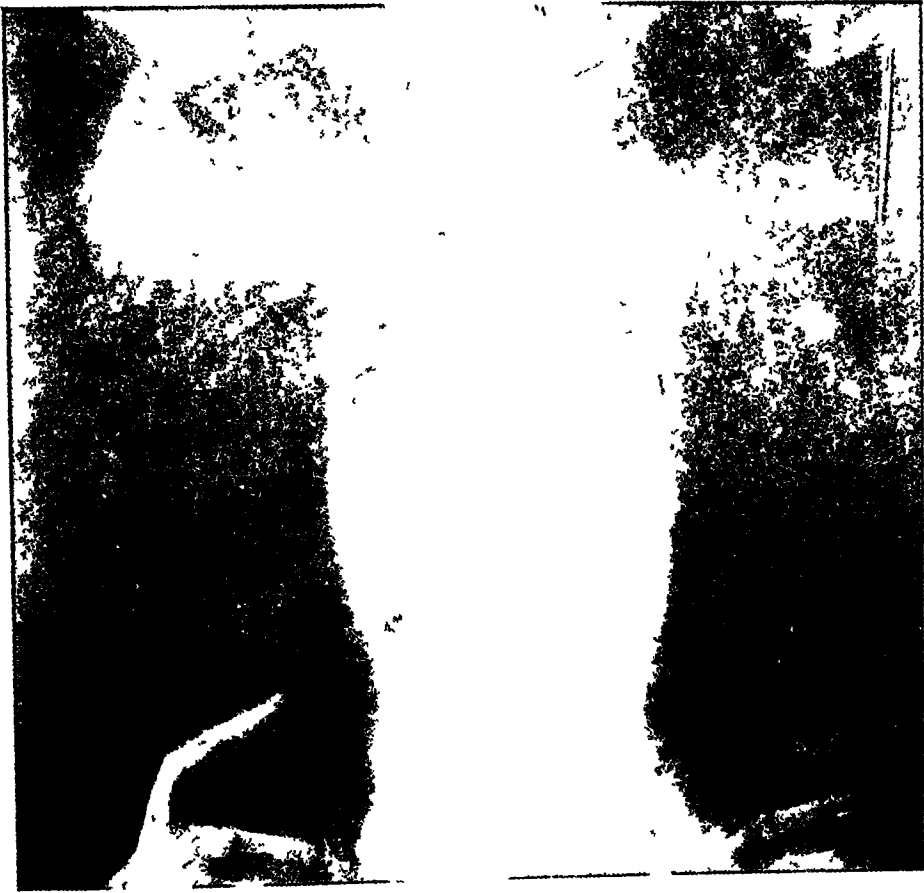


FIGURE 3 H I C July 11 1927 Apparently normal chest with heart in correct position

Asheville it was hoped that the patient was suffering from some form of "atypical tuberculous pleurisy" though the transmitting physician had had no opportunity for thorough examination of the patient owing to the continuing hemoptysis. Here is a patient then of 42, an inveterate smoker of cigarettes for 25 yrs., 46 lbs underweight, though only 10 lbs to 15 lbs under his personal average, presenting the history of a harassing cough developing without a coincident respiratory infection, this cough at first dry with later some muco-purulent expectoration, and repeated hem-

optysis with daily temperature to 99<sup>5</sup> or 100 F. As you note, X-ray films made prior to any blood spitting, but because of suspected tuberculosis revealed an essentially normal picture, with the heart in its proper position. Some ten weeks after the hemoptysis when I saw the patient, the entire picture was changed but it was not at first apparent what was the true condition. For two weeks after arrival patient was not subjected to thorough chest examination for fear of causing return of the hemoptysis. The blood picture had immediately cast suspicion upon the probability of this



FIGURE 2 M. L. H. March 16 1927 Complete clearing of left lung

soon merging into flatness from 3rd rib down—anteriorly and posteriorly—left being clear

*Auscultation*—Showed tracheal breath sounds over rt upper lobe—absent breath sounds elsewhere on rt—exaggerated inspiration over entire left lung—no adventitious sounds anywhere

*Films*—(Fig 4)

*Urimalysis and Sputum Exams*—Negative

*Blood*—Hbg 70% RBC 3,840,000 WBC 9,140 Differential—uninforming Wassermann—negative

You will note in the film of July 12th (Fig 3) that we have an essentially normal chest picture. The roentgenologist, Doctor John H. Edmond-

son, who made the films reported as follows

*"Chest Rt Side* Some increased fibrosis is noted in the hilum, which contains a number of calcifications in its upper portion

*Left Side* Hilus, bronchioles and parenchyma present nothing from X-ray standpoint suggestive of pathology

*Heart*—Centrally placed and about normal in size

There is no impairment to diaphragmatic excursion. This case does not present the appearance of a tuberculous manifestation." When sent to

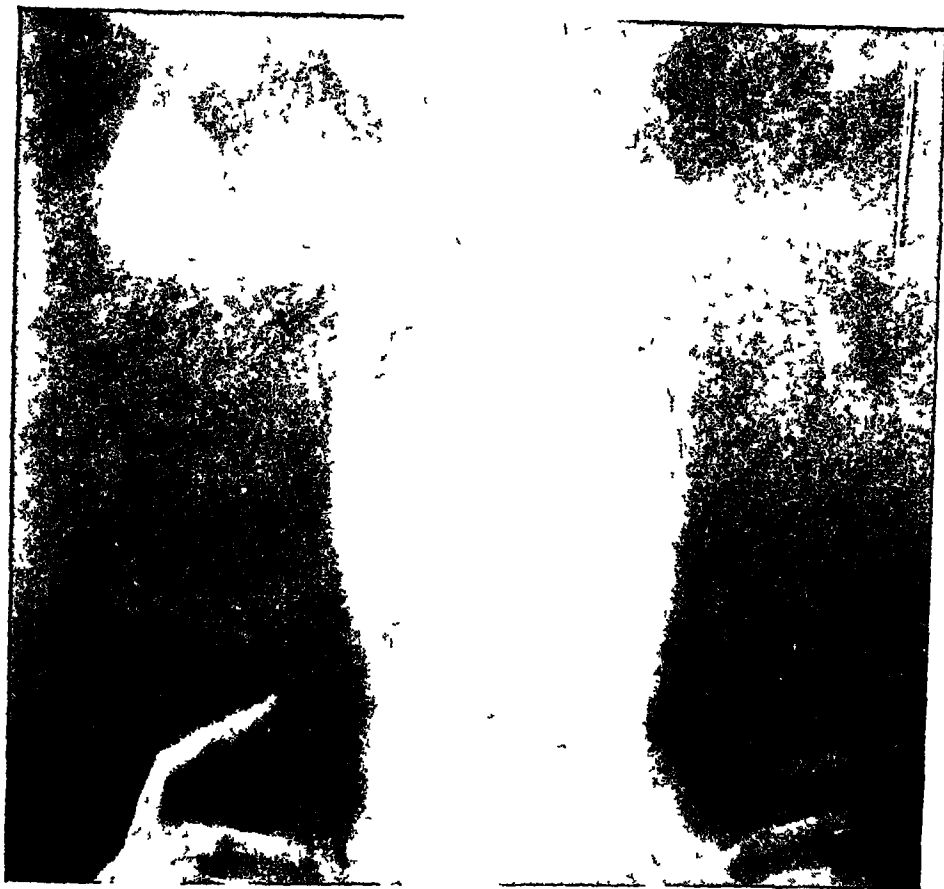


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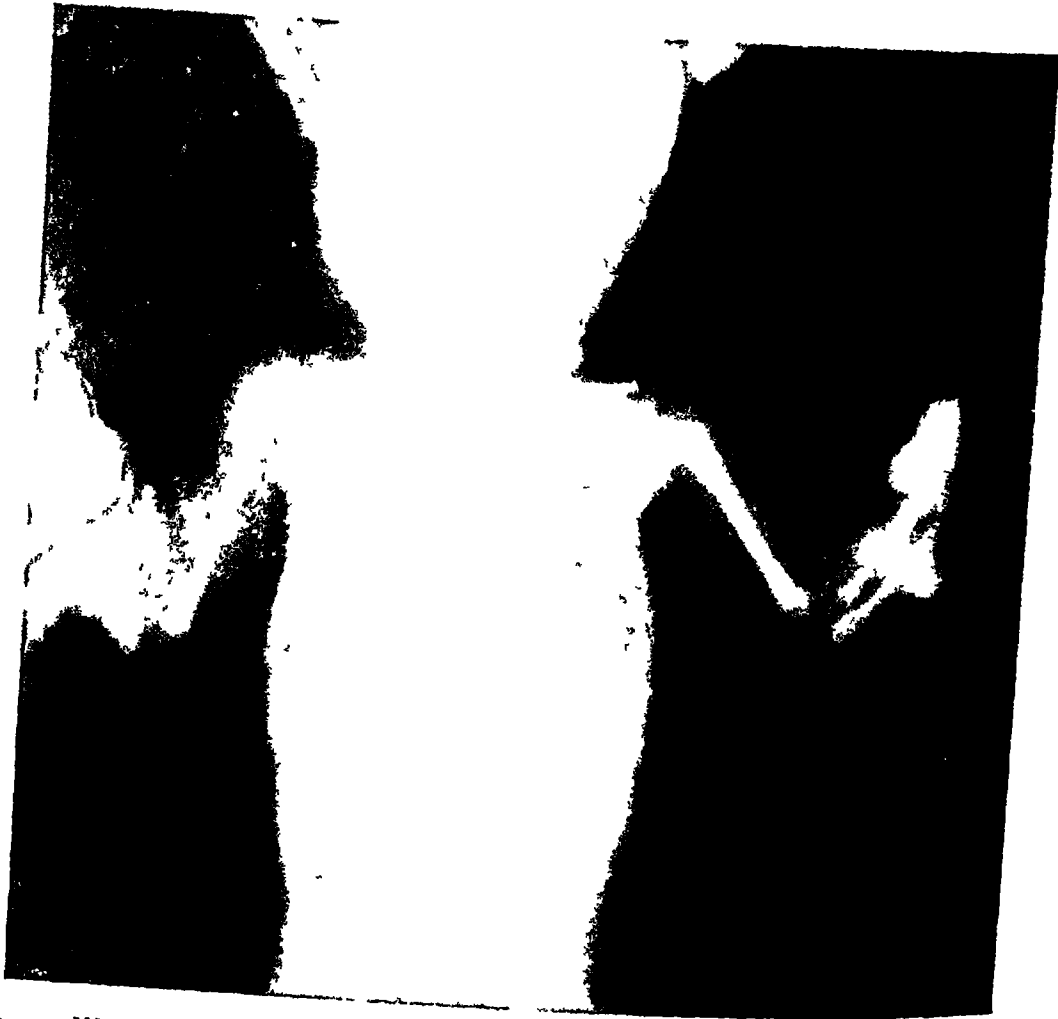


FIGURE 4 W. F. C., Oct 18, 1927 Complete opacity of right chest with heart and trachea pulled to right side of thorax

being a case of pulmonary tuberculosis. Such a degree of anemia as 3,800,000 R. B. C. in a patient who showed no demonstrable tuberculous pathology only three months previously and who had not lost, all told, in two months over a pint of blood did not lend weight to the possibility of tuberculosis.

The patient was brought to the office because of a suspicion that a more serious state of affairs was going on than tuberculosis. The clubbing of the fingers seemed to be increasing, the temperature showed no change under bed rest on a sleeping porch,

he had been told that it was not proven that he had tuberculosis, that all sputum tests had proven negative and the risk of further hemorrhage was thought to be small. The films showed, as you see, a complete dextrocardia (of a heart 3 mos. previously in a normal position), a trachea pulled well to the right, and uniform massive density of the entire right chest. With the physical findings as outlined earlier, it was now apparent that we were dealing with a case of complete atelectasis of the right lung. The cause of this it was difficult to ascertain. Pulmonary hemorrhage from

tuberculosis with organization of a clot resulting in plugging the main stem bronchus did not seem likely—particularly as there was no evidence of tuberculosis. The general appearance of the patient, the rapid clubbing of the fingers, especially the anemia out of proportion to probable tuberculosis, the persisting P M temperature daily and the failure of the patient to improve caused the suspicion of malignancy. A tentative diagnosis then of endobronchial malignancy was made which seemed to explain the whole history from harassing dry cough with subsequent hemoptysis to the development of massive atelectasis and bronchoscopic examination urged. The patient was referred to Dr Chevalier Jackson of Philadelphia who reported as follows:

"Mr C was referred to us with the opinion that he did not have pulmonary tuberculosis and also that the right lung was collapsed. Our bronchoscopic examination confirmed both of these opinions. As you will see by the enclosed report of bronchoscopy the collapse was due to the right bronchus being plugged with a white pedunculated tumor which had the appearance of being malignant. A specimen taken bronchoscopically confirmed this tentative bronchoscopic diagnosis. Dr B L Crawford who examined the specimen histologically reported the growth to be carcinoma. As the growth is at the root of the lung in the main bronchus external surgery is not indicated. I could easily remove the mass of the growth with biting forceps but mutilation of a cancer does not seem to be good surgery and especially so in this case,

because carcinoma of the lung is particularly susceptible to arrest by deep roentgen therapy."

#### PATHOLOGICAL REPORT

"Specimen consists of several small pieces of grayish tissue the largest measuring 7 mm in its greatest dimension.

*Histology* Sections show the fragments of tissue to be largely composed of masses of large cells with hyperchromatic nuclei. The cells vary greatly in size and shape and are undifferentiated and many show mitosis. There are small fragments of necrotic tissue present and only a very small piece of stratified squamous epithelial mucosa is attached to one of the fragments of tissue.

There is no question that the lesion is a malignant neoplasm and the cells are considered to be epithelial, but they are not sufficiently differentiated to indicate the type of epithelium from which they are arising.

#### *Diagnosis—Carcinoma "*

Patient returned to his home in Birmingham for deep X-ray therapy. This failed to accomplish anything save the alleviation to some extent of the dyspnea which undoubtedly must have become progressive. He died April 14, 1928. A summary of the pathologist's report by Dr George S Graham is as follows:

#### PATHOLOGICAL REPORT

##### *"Anatomical Diagnosis*

- I—Carcinoma of right bronchus. Metastases in liver, spleen, pancreas, cecum and in bronchial, mesenteric, para-aortic lymph nodes.

- 2—Atelectasis of right lung
- 3—Chronic adhesive pericarditis
- 4—Chronic adhesive pleuritis
- 5—Pleural effusion (right)
- 6—Postmortem or agonal intussusception of the ileum”

*“Lungs—*Sections through the tumor show a type cell of epithelial characters. It is rounded or polygonal in shape varying at times to columnar. It is arranged in columns which sometimes show irregular central spaces suggesting lumina. Mitosis occurs but is only occasional. In large areas it has undergone complete necrosis. In one block a thick tumor mass is shown beneath a bronchial lumen. It has replaced all the normal structures. Masses of tumor cells occur within the lumen of a large vessel in one block. The blocks show little of the alveolar structures of the lung. When

such are present they are being invaded by masses of tumor cells”

*Comment—*The histology of this tumor indicates origin from the bronchial mucous membrane.”

The mechanism of the atelectasis in this case is quite apparent. A malignant growth starting in the main right bronchus produces an harassing cough, followed by hemoptysis as the tumor ulcerates. The hemoptysis is repeated and finally either a clot organizes or the tumor growth reaches sufficient size to block the main stem bronchus. Coincident with the general symptomatology of progressing malignancy, the air in the right lung is fairly rapidly absorbed because of the blocked bronchus and the picture of massive atelectasis is found. Bronchoscopic, pathologic, and autopsy examinations confirm the diagnosis.



# Thymoma of Lymphosarcoma Type\*

By EBEN E. SMITH, M.D. F.A.C.P. *Lieutenant Commander Medical Corps,  
U. S. Navy*

THYMIC tumors are of considerable interest pathologically because of their comparative rarity and difficulty in classification and clinically they are of equal interest because of the diagnostic and therapeutic problems involved. A review of the literature suggests that these tumors are probably more common than recorded case reports would indicate. The following case is therefore reported because it presents several features of unusual interest.

A. M. H. was admitted to the U. S. Naval Hospital Norfolk, Virginia, February 1st, 1928. Diagnosis: Hyperthyroidism. Chief complaint: Difficulty in breathing, choking sensation in throat, cough, pain on swallowing and swelling in neck. Family history: Negative. Past history: Patient has lived all his life in and about Arkansas and his parents before him have also. He has never seen any goiter in that vicinity. He has always been well at home. Since joining the Marine Corps, the only sick days have been for tonsillectomy, September 8th, 1927, with seven days on the sick list. Had broken arm 1919. No other injuries or operations. Nothing has occurred to him or to his family recently which could be considered a precipitating event. Has lost some weight. Best weight 132 pounds, average 125 pounds. Present weight 122 pounds. Head—Negative. Ears—Negative. Eyes—Negative, states that they feel a little

luggish since onset of present illness. Nose—Negative. Cardio-respiratory—No symptoms referable to this tract prior to present illness. Gastro-intestinal—Negative. Genito-urinary—Had gonorrhea in 1923. Neuro-muscular—States that he has been nervous for a year or more. He is an electrician and sometimes has had to hold a screwdriver in both hands to make it steady enough to use. This has passed off since present illness. Marital—Single. November 7th, 1927 patient was examined prior to transfer and found to be physically fit. On November 12th, 1927 record shows an attack of epistaxis that was controlled by adrenalin. Patient was again examined for transfer, prior to November 23rd, 1927 and was found to be physically fit.

Present illness: Began gradually about two months ago, about December 7, 1927, while on transport en route to Nicaragua. The first thing patient noticed was a choking sensation and difficulty in breathing while lying down. This was not severe and was relieved by lying on his side or sitting up. On December 17th, ten days after onset, patient, while asleep, was awakened suddenly by an acute attack in which he had a sensation of having his breath completely shut off and finally got his breath by sitting up and leaning forward. From this time until about the middle of January, patient was relatively free from respiratory symptoms. He noticed some difficulty following exertion and was a little weak but had very little trouble sleeping. He started to cough during this period but paid no attention to it at first. It was a dry, non-productive cough and was not relieved by sitting up. The cough became worse, however, and about the middle of January pa-

\*From the Department of Pathology, U. S. Naval Medical School, Washington, D. C.

tient noticed that his neck was swelling. After this, the cough did not progress but stayed about the same and the attacks of difficult breathing started again, mostly at night. Sometimes, coughing relieved the respiratory embarrassment. After the middle of January, the cough improved but the neck enlarged gradually, "seemed to grow larger daily" and the respiratory embarrassment became more pronounced. At present he cannot get his breath while lying down and is comfortable only while sitting up with his head forward and he can sleep only in this position. Patient has had no pain except in the muscles of his neck. He states he was nervous before present illness started but has been relieved since. He has noted no changes in his eyes. He thinks that his heart beats faster than it used to, especially when he coughs, and he has a tendency to become a little nervous.

**Physical examination** General—Patient sitting up in bed and leaning forward. He is well developed and nourished, has a worried expression and respiration is labored. There is a swelling at the base of his neck anteriorly. No other gross abnormalities noted. T—99.6 P—124 R—24 Head—Negative. Eyes—Pupils are regular and react normally to light and accommodation. Sclerae are normal. No exophthalmos or lid lag. No failure of convergence. Slight lateral nystagmus. Consensual reflex normal. Ears—Negative. Nose—Negative. Mouth—Mucous membranes negative. Teeth in good condition. Tonsils absent. Throat slightly congested. Neck—Anterior and posterior cervical glands are not felt. Anteriorly above the sternum, the neck is enlarged as by the thyroid. Palpation shows this to be a soft but definite enlargement caused by a mass apparently arising from behind the sternum. It extends upward on both sides of the neck and across the trachea in front of the neck and does not move when patient swallows. The isthmus of the thyroid can be palpated behind the mass when patient swallows. The mass does not appear to be attached to the trachea, larynx, or thyroid gland. Over the trachea, it is about three-quarters of an inch in thickness. Thorax—Normal in size, shape and con-

tour. Normal movement and expansion upon respiration. Tactile fremitus is decreased anteriorly over an area extending about four inches on either side of the sternum and including the heart area. Over the back there is a slight increase in fremitus throughout. To percussion, there is an area of dullness and flatness over the entire pre-sternal area. The breath and voice sounds are somewhat decreased over an area corresponding to the dull area. Expiration is increased, there are many squeaking and sonorous râles all over the chest heard best in the resonant area. Posteriorly, there is a dull note completely across the back above the seventh ribs. Below this line, the note is hyperresonant. There seems to be no corresponding demarcation in the fremitus or breath and voice sounds, all of which are increased. Râles corresponding to those heard anteriorly are heard throughout. The area of dullness shifts with a change in the patient's position. Heart—Apex impulse not seen or felt. Heart cannot be outlined by percussion. Heart sounds are distant, rapid and weak. No arrhythmia. Blood-pressure—Left arm 112/80, right arm 114/82. Abdomen—There is a marked dilatation of the superficial veins. In standing position the superficial veins of the abdomen and thorax become engorged and stand out like cords. No tenderness or spasm. No masses. Liver, spleen and kidneys not felt. Genitalia—Normal adult male. Extremities—Evidence of old fracture of arm. There is no clubbing of the fingers, no ataxia, and no tremor. The veins of the extremities are not dilated. Reflexes—Present and active. There are no hemorrhoids.

February, 2, 1928 Basal Metabolic Rate Plus 95% Note "The above findings cannot be considered accurate, but only as an approximation. A technically perfect test is impossible in that the patient cannot lie down, has a persistent cough and the respiration is of the extreme asthmatic type." Complete blood count. Red blood count 3,850,000. White blood count 5,700. Haemoglobin 75%. Color index 0.9. Polys—66. Lymphs—32, Monos—2. Ophthalmoscopic examination negative. X-ray exam-

mation of the chest "There is a massive enlargement of the mediastinal shadow, so that the shadow extends to the level of the middle third of the clavicle, on the right side the border of the shadow is convex. There are no irregular glandular enlargements outside of the shadow. The lung detail is poor, but there appears to be considerable peribronchial thickening in both lungs. The upper border of the shadow below the 1st rib narrows down and then there is an expansion of the shadow extending upwards into the neck on each side, in the lateral view there appears to be a

small space between the anterior limits of the mass and the sternum (Fig 1). Fluoroscopic examination "There is a large shadow occupying the mediastinal space. In the posteroanterior view the heart cannot be seen. rotating the patient the heart is located pushed to the left and backwards. The tumor mass does not pulsate. Impression —Tumor of mediastinum, probably sarcoma."

February 3, 1928. Diagnosis changed this date to sarcoma mediastinum, and patient was transferred to the U. S. Naval Hospital, Washington, D. C., as an emergency



FIG 1 Taken three days before death, obtained with difficulty due to respiratory embarrassment and lateral view is unsatisfactory for reproduction

case, for deep X-ray therapy Patient was admitted to the U S Naval Hospital, Washington, D C, Sunday morning, February 5th and died within 24 hours from cardio-respiratory embarrassment

#### AUTOPSY REPORT

Autopsy two hours after death General Body is that of a white male Height, 67 inches Weight approximately 125 pounds Age, 25 years Body still retains some warmth Rigor mortis is absent There is some lividity, particularly over the sides, chest, around the shoulder girdle, neck and face Ears are cyanotic Finger nails cyanotic No edema No abdominal distention Neck is swollen, somewhat boggy, more so on the right In the mid-line, just above the sterno-clavicular articulation, a tumor can be felt Superficial veins of chest are enlarged No definite caput medusae Axillary glands just barely palpable No glands or swelling noted in the supra-clavicular fossae No cervical glandular enlargement Eyes—Pupils moderately dilated Fresh blood draining from nose and mouth Teeth in excellent condition, all present One vaccination scar insertion left deltoid

Chest On opening chest a large tumor mass is exposed, situated almost symmetrically in the mid-line Entire mass, including heart, lungs and neck structures, removed intact See Figs (2) and (3) Weight of entire mass, Gms 4400 Net weight of tumor mass, Gms 3110 Dimensions Length, 30.0 cm, Breadth, upper chest, 14.0 cm, Breadth at base of diaphragm, not including extensions along diaphragm, 22.0 cm, Depth, at bifurcation trachea, 12.0 Origin not definitely determined, but apparently originating in anterior mediastinum Mass extends into neck to isthmus of thyroid, infiltrates adjacent visceral and parietal pleura, especially of the diaphragm, and surrounds the heart to the extent that it cannot be identified on anterior exposure In the upper half of the mediastinum it is intimately adherent to the sternum, but there is no erosion Posterior wall in mediastinum uninvolved Tumor is firm, gray and has a lobulated smooth surface Section shows a homogeneous tissue

almost white and friable with no gross evidence of reticulum or fibrous septa and with occasional small hemorrhagic areas of discoloration (See Fig 4) Considerable clear fluid is present in both pleural cavities Lungs uninvolved except that tumor has infiltrated the pleura adjacent to tumor, are crepitant, and appear normal except for some congestion Pericardial cavity distended with increase of clear fluid, and parietal pericardium is granular from tumor invasion A small area of the posterior wall is uninvolved Heart distinctly smaller than normal and is flabby Left ventricle contracted, right dilated Valves, coronaries and aorta normal The ascending aorta, the aortic arch, the superior vena cava and the pulmonary vessels are incorporated in the tumor mass The intra-thoracic portion of the branches of the arch and the branches of the vena cava are also surrounded and apparently compressed and the venous system is engorged The tumor infiltration appears to invade the adventitia of the vessels but not the muscularis The esophagus is uninvolved and the trachea and its main branches occupy a depression on the posterior surface of the tumor They are not infiltrated At the root of the lungs, however, both bronchi and vessels are surrounded by tumor

Abdomen Peritoneum smooth and glistening Slight, if any, increase in fluid Omentum normal All vessels congested Gastro-intestinal Tract—Nothing unusual noted in stomach and intestines, other than congested vessels There are many palpable nodes in the mesentery which are small, discrete and relatively soft A few in the region of the celiac axis are enlarged The appendix is retrocecal and quite long, measuring 15.0 cm Liver—Weight, Gms 1530 Chocolate in color Liver border reaches costal margin Surface smooth and glistening On section, congested Lobulation is not accentuated Ducts are patent Gall bladder contains a few cc of mucoid bile Pancreas—Weight, Gms 90 Appears normal Spleen—Weight, Gms 270 Slate blue in color Rather soft Capsule is smooth On section follicles are accentuated Kidneys—Readily mobilized Capsules strip

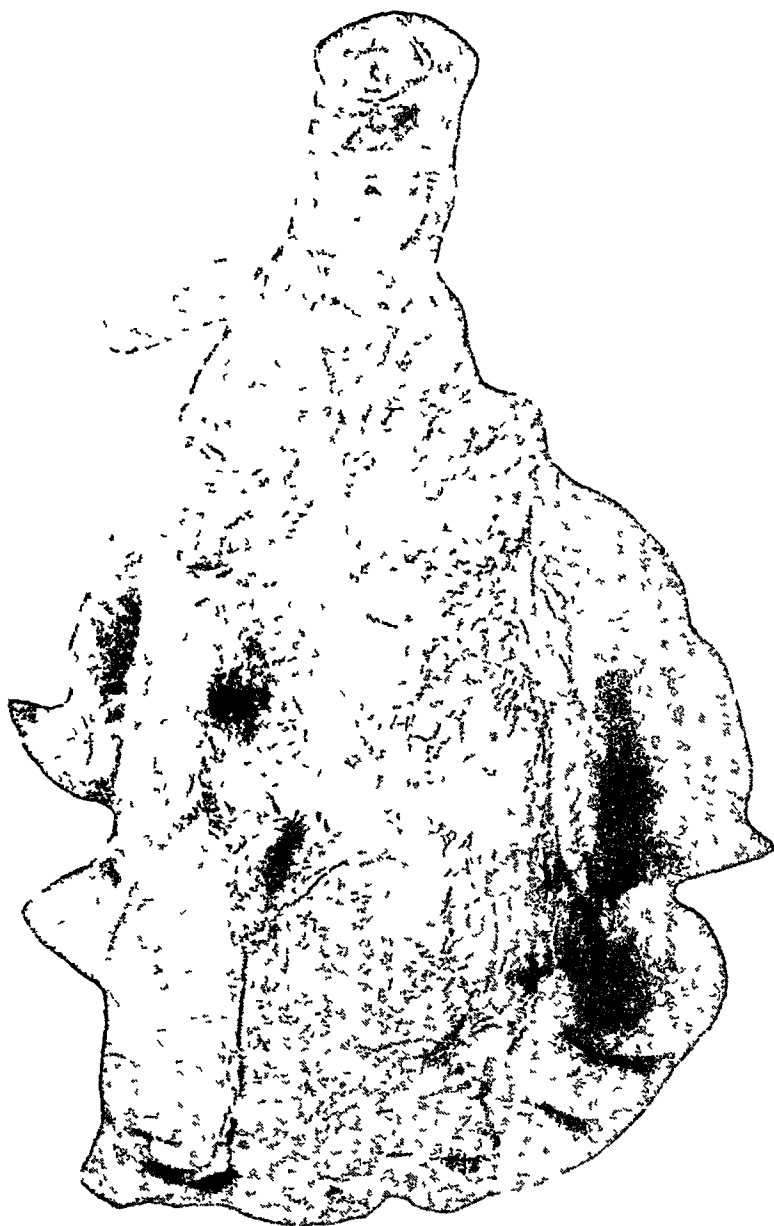


FIG 2 Anterior aspect of entire mass including lungs, tongue, trachea, thyroid gland and esophagus. Mass was adherent to sternum at point where grey area shows on mass.

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FIG 2 Anterior aspect of entire mass including lungs, tongue, trachea, thyroid gland and esophagus. Mass was adherent to sternum at point where grey area shows on mass.



FIG 3 Posterior view of entire mass, includes lungs, trachea, upper section of esophagus, descending aorta and reflection of tumor growth along diaphragm The discoloration is due to improper fixation



## Thymoma of Lymphosarcoma Type



FIG 4 To show character of cut section of tumor

readily, leaving a mahogany-red smooth surface. On section cut surface is distinctly congested, and dark red in color. Pyramids are accenuated. Cortex measures 7.0 mm. Left kidney, weight, Gms 170. Right kidney, weight, Gms 150. Ureters are not dilated. Bladder contains a small amount of clear urine. Adrenals appear normal.

#### MICROSCOPICAL REPORT

**Heart** Free from infiltration. There is some atrophy of the muscle cells with deposition of brown granular pigment.

**Lungs** Negative except for a fairly marked degree of passive congestion. One section includes area of pleura that is infiltrated with tumor cells. The infiltration is limited to the pleura and adjacent lung field

and resembles in type that found in the tumor. There is a mass of the tumor on the pleura the cells of which invade and practically replace the pleura, a few fibers of which are contained in the tumor. The cells infiltrate entirely through the pleural layer and into the alveolar walls and the strands of connective tissue entering the lung from the pleura. (See Fig 5)

**Liver** Shows congestion, granular degeneration and pigmentation, more marked in the central zone.

**Pancreas** Shows vascular engorgement.

**Spleen** Structure is relatively normal. Germ centres are large, not very compact, and not particularly active. Centrally some have some nuclear debris. Stroma not increased in amount. Vessels and sinuses

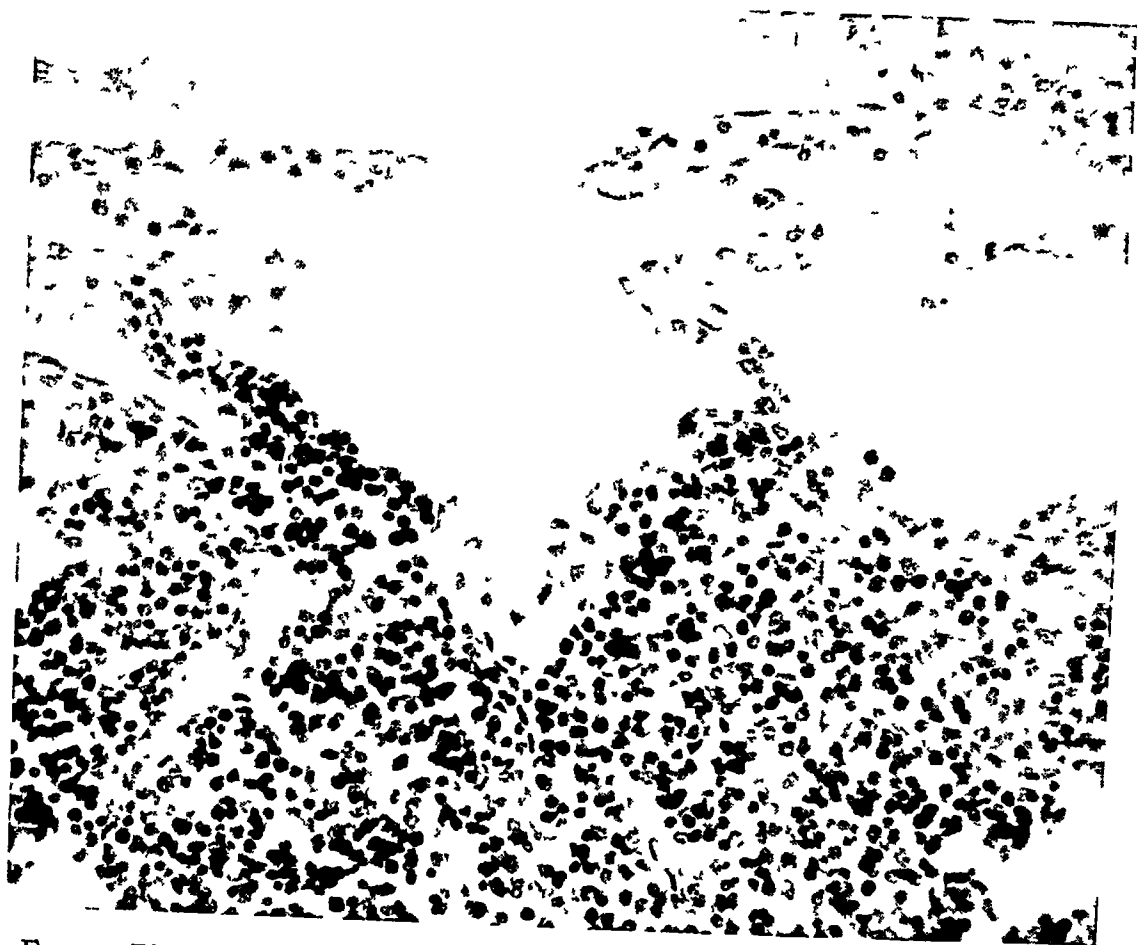


FIG 5 Photomicrograph of pleural involvement showing character of tumor cells and invasion of pleura and adjacent area x405

congested There is an increase of reticulo-endothelial cells

Kidney Shows marked vascular congestion

Adrenal Capsule is thickened and has a considerable degree of infiltration with lymphocytes

Thyroid Some epithelial hypertrophy is present, but there is no hyperplasia. Some undifferentiated epithelium occurs. There is some lymphocytic infiltration in the stroma.

Tumor Tumor consists predominately of cells of lymphocyte type with no structural differentiation and relatively little stroma. It is well vascularized and no necrosis is evident. Section through a lobulated mass at the border of the tumor shows tumor growth arranged in a whorl like structure, but here as elsewhere there is no attempt at germ centre formation. The cells consist predominantly of lympho-

cyte type but there are many immature cells of lymphoblast type diffusely distributed (See Fig 6). Reticulum is comparatively fine in structure and varies somewhat in arrangement. In some areas it presents an irregular meshwork (See Fig 7), while in other areas there is tendency for the strands to take a parallel course and for the tumor cells to be arranged along the strands as if attached to a basement membrane. No epithelium or hyaline structure suggestive of Hassall corpuscle formation and no polyhedral reticulum cells or myeloid giant cells, such as have frequently been reported in this class of tumor, are found in any of the sections.

Lymph nodes Mediastinal node shows a central caseation and peripheral zone cannot be differentiated from tumor tissue. Mesenteric node shows a marked reticulo-endothelial hyperplasia and lymphoid tissue

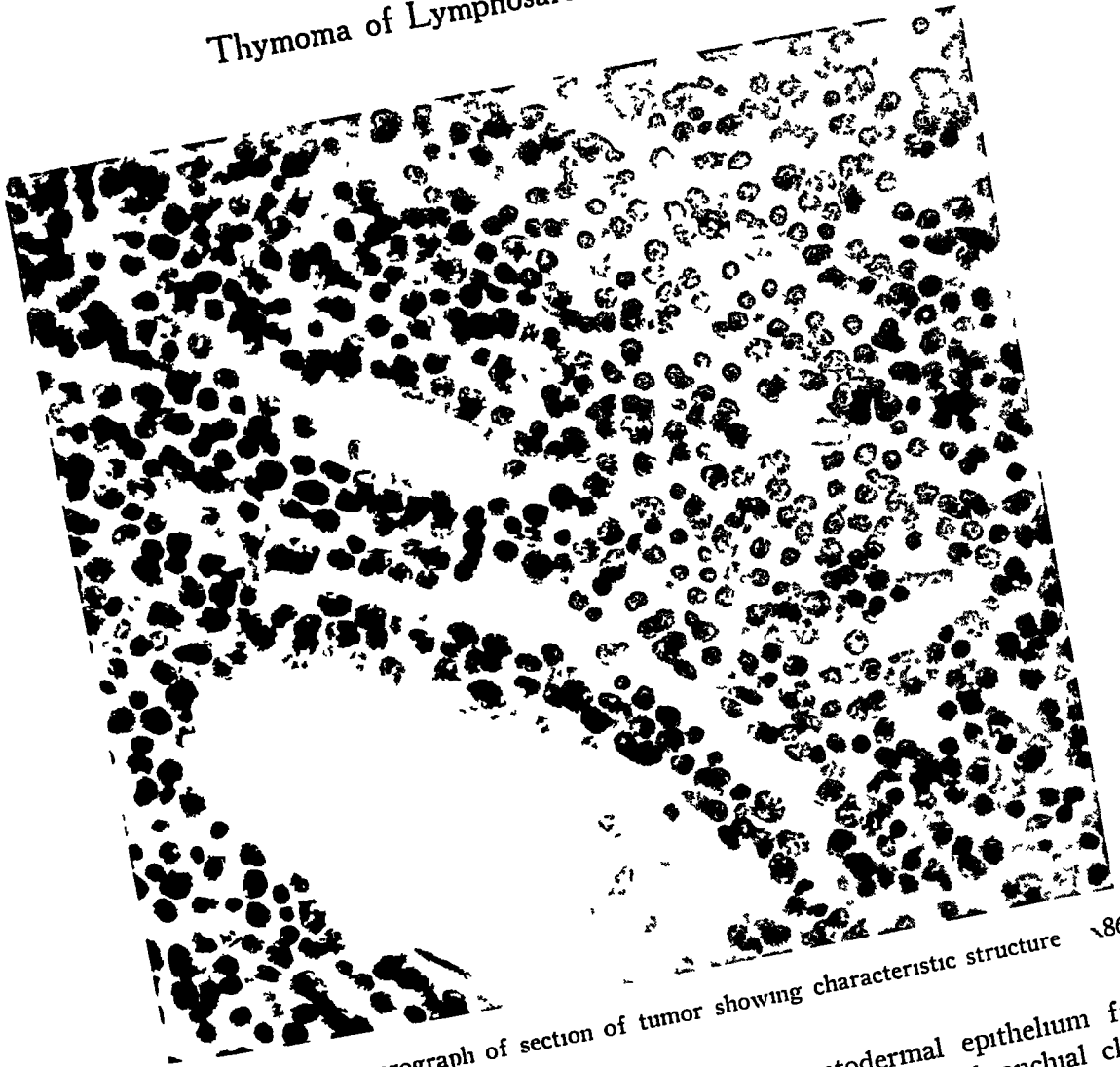


FIG 6 Photomicrograph of section of tumor showing characteristic structure  $\times 860$

cannot be distinguished from tumor growth except that it is differentiated into germ centres and the immature type of cells is less common

**Pathological Diagnosis** Lymphosarcoma, mediastinal, massive, thymus /vascular obstruction, great vessels of chest, pressure Myocardial insufficiency

Classification of tumors of thymic origin awaits final decision as to the histogenesis of the various types of cells found in the thymus and acceptance of a uniform nomenclature. There is essential agreement that the thymus originates as paired invagina-

tions of entodermal epithelium from the third and fourth branchial clefts. As the gland evolves, embryologically, lymphoid tissue becomes dominant in the picture. According to histologists the original entodermal epithelium persists in the adolescent thymus as (a) reticulum forming a fine meshwork syncytium in which the lymphoid cells are incorporated and as (b) clumps of concentrically arranged flat cells known as Hassall corpuscles. Opinion is still divided as to the origin of this lymphoid tissue. Pappenheimer (1) and others maintain that it originates from the original ento-

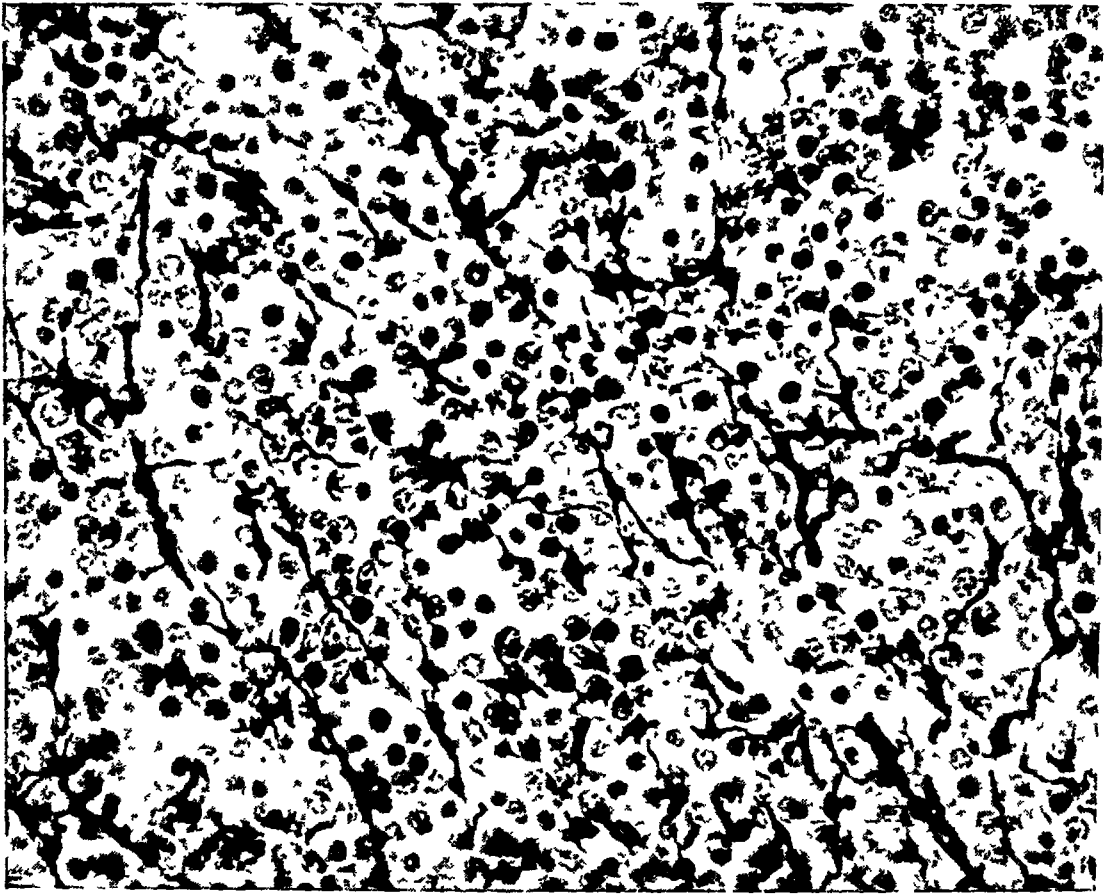


FIG 7 Photomicrograph, reticulum stain, showing irregular distribution of reticulum and cells  $\times 860$

dermal epithelium. This author suggests the probability that these lymphoid cells may originate from the reticular endothelium even in adult life. Danchakoff (2), Maximow (3), and Hammar (4), among others, maintain that these lymphoid elements are true lymphocytes of mesodermal origin that infiltrate the thymus in early embryonic life.

Whichever opinion is correct, a review of the literature indicates that thymic tumors manifest marked diversity of type. On one extreme is the rare pure epithelioma and on the other extreme is the more common lymphosarcoma with no characteristic epithelial structure in evidence. More

commonly, both elements are represented with the lymphoid type of cell usually predominating and the histopathological picture is correspondingly confused. Ewing (5) proposes the following practical classification of these tumors: "(1) Lymphosarcoma or thymoma, composed of a diffuse growth of round, polyhedral, and giant cells. The source of this tumor is probably the reticulum cell, but lymphocytes are present in abundance. (2) Carcinoma arising from the reticulum cells. To these may be added very rare and somewhat questionable cases of tumors attributed to the stroma and called (3) spindle-cell or myxosarcoma."

The interesting features of this case are (a) The unusual size of the tumor, exceeding that of any found on record. Sternberg (6) reports an unusually large lymphoid tumor of the thymus that in several respects resembles this case. It measured 22 x 13 x 6 cm and is the largest tumor found on record. His patient was 16 yrs old. Duration of symptoms prior to death was three weeks which is the most rapidly fatal case found recorded. The pericardium was found infiltrated firmly encasing the heart. There was a slight but not marked general enlargement of the lymph nodes. His case differs in that post-mortem examination of the blood revealed a leukemic blood picture. (b) The type of cell. There is no suggestion of epithelial or reticulum cells, no giant cells are found and lesion does not resemble Hodgkin's granuloma. Cytologically this tumor corresponds most nearly to a pure lymphosarcoma. (c) Tumor was limited to growth by direct extension and invasion of neighboring tissue while present was not marked. The lymph nodes found in the mesentery are not suggestive of metastases. These nodes were definitely hyperplastic but not more so than is observed commonly in conditions where the question of malignancy is not considered. The tonsillectomy performed one month before onset of symptoms may be of significance. The tonsils were not examined histologically. The surgeon noted nothing unusual except that they were hypertrophied and cryptic and patient had a normal convalescence.

The tumor reported conforms with the type usually found originating

from the thymus and falls in the lymphoid group which is more common than the epithelial type, differing however, in that the cells are uniform rather than diversified in type and no epithelial structures are included. It extended from the thyroid to the diaphragm and originated in the anterior mediastinum. It was roughly pyramidal in shape, with the base down, had a firm consistency, surface was somewhat lobular but cut surface was relatively homogeneous, surrounding and compressing rather than invading the great vessels, trachea, bronchi and heart and was limited to the thoracic cavity. The clinical manifestations also conform with the usual findings, namely, a relatively rapidly growing tumor causing respiratory and circulatory embarrassment resulting in death approximately eight weeks after onset of symptoms. Two months duration is not rare with this class of tumor but the average is longer. Death within three weeks (6) and five weeks (7) has been reported. A dry non-productive cough is commonly the first symptom manifested by these tumors and with its onset or later dyspnea develops. In this case dyspnea antedated the cough but both were present and caused the chief embarrassment the patient suffered.

Development of collateral circulation due to pressure upon or thrombosis of the vena cava has been reported (8), (9), (10), (11), (12), (13) and (14), among others. No thrombosis was present in this case but the pressure was sufficient on the superior vena cava, to cause a developing collateral circulation. This was quite evident during life but was in-

conspicuous at autopsy suggesting recent onset and only partial obstruction. Cardiac function was further embarrassed by the tumor infiltration into the parietal pericardium which was so extensive as to practically destroy the elasticity of this membrane.

Erosion of the tumor through the anterior chest wall (7), (15) and (16), or of the thoracic vertebrae (17), (18), (19) may occur. It was not present in this case. However, the tumor had to be cut from the sternum and bony erosion would seem a reasonable probability had the patient survived for a longer period. The blood picture was normal. Cases are on record manifesting a lymphatic leukemia, (12), (16), (20) and probably (6) in which the type of leukemia is not specified. Tumors or other abnormalities of the thymus occur in association with myasthenia gravis in sufficient frequency, approximately 50 per cent (21) to suggest that it is not a mere coincidence. A typical case is on record in which a carcinoma of the thymus was found at autopsy (22) and another case responded favorably to X-ray treatment to a thymus tumor (22). These tumors may be confused with Hodgkin's clinically and doubtless have been erroneously diagnosed such. Limitation to the mediastinum should suggest the possibility of a thymic origin. Even histopathologically the tumor may resemble the granuloma of Hodgkin's (5).

There are clinical features that suggest a differential diagnosis between tumors that are carcinomatous and those that are sarcomatous in type. Biopsy is the only positive means of

differentiation. Carcinoma usually occurs in later life, after 40, while sarcoma occurs predominantly before 25, suggesting a possible relationship with a disturbance with the normal involution of the thymus which occurs with adolescence. Carcinoma does not tend to reach such large size and is not so rapid in growth. However, epithelial tumors of considerable size may occur (17), (20) and (23). Sarcoma may erode the sternum while involvement of the thoracic vertebrae has been by carcinoma. No definite exception to this localization has been found in any of the case reports. Carcinoma has a greater tendency to metastasize. Sarcoma with an associated lymphatic leukemia is an exception to the tendency of sarcoma to remain localized in the mediastinum. Sarcoma compresses rather than invades the great vessels, trachea and esophagus. Carcinoma is more likely to invade these structures. Consequently thrombosis and terminal hemorrhages are more frequent with carcinoma.

Diagnosis is greatly facilitated by X-ray. Exposure in the lateral position is particularly useful. These tumors, if not large, do not cast a dense shadow and a negative finding may confuse rather than assist in the diagnosis. The prognosis, as with malignancy in general, is unfavorable. Early intensive treatment with X-ray and radium has given some hopeful results and the lymphoid type may be especially responsive (11), (15), (16), (22) and (24). Surgical removal has been suggested but there is no record of this having been done. Palliative relief of pressure upon the

trachea has been obtained by dividing the manubrium and separating it from the sternum (9).

#### ACKNOWLEDGMENT

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# A Further Experience in the Etiology and Treatment of Encephalitis

By S R SALZMAN, M D, *Toledo, Ohio*

**A**T this time, when another epidemic of influenza is spreading throughout the country, we may expect again the recurrence of some cases of encephalitis of the so-called epidemic type

Because of the high mortality and still higher morbidity and the marked economic loss following this disease, everything which may hold out any hope in the treatment of this disease deserves consideration by the medical profession

This is my excuse for again calling attention to the probable association between gall-bladder disease, or more particularly, gallbladder toxemia, and this type of encephalitis

Previously I reported (*Archives of Neurology and Psychiatry*, Nov, 1925, Vol 14, pp 638-648) ten cases of encephalitis treated according to the theory that the gallbladder is responsible for this disease, and the results were recorded. Only a few of the outstanding cases were reported in this article. In all, I have had a total of about forty cases, most of them of the endemic or sporadic type

However, because of an experience during the recent epidemic, I am reporting one outstanding case in order to again call attention to the

remarkably clean-cut results obtained by this method of therapy

The question naturally raised following the report of the first series of cases was "Are these cases of encephalitis the true epidemic, lethargic encephalitis, associated with epidemics of influenza?"

My comment at that time was that since the text books on the subject scarcely mention encephalitis as a clinical entity, that only two cases had been reported in a search of a number of text-books on neurology, it is probable that most of the cases, if not all seen at this time, are really cases of encephalitis of one type, despite the variations in the severity of the cases

However, the case presented here occurred during an epidemic and following a rather severe case of influenza, and leaves little room for doubt that it is the well recognized type of epidemic encephalitis

It may be well to again call attention to certain facts which speak against encephalitis being an infectious, epidemic disease

These points were noted in the original article

1st The evident involvement of the brain by way of the blood stream. Most, if not all, infections into the cerebral spinal axis are by way of the



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1st The evident involvement of the brain by way of the blood stream

Most, if not all, infections into the cerebral spinal axis are by way of the

lymphatics, through the nasal mucous membrane, or nasopharynx

2nd The rather prolonged prodromal period present in the majority of the cases. As noted, this prodromal stage cannot always be determined until the patient recovers and is mentally clear enough to give a more accurate history than can be obtained during the acute illness

3rd The marked variability in the duration of the illness. Practically all contagious diseases are self-limited. Their duration is fairly uniform in all cases. Encephalitis has no uniformity, no two cases are alike, and the duration may be from a week to months or even years, suggesting rather strongly the continuation of a toxic factor rather than a bacterial disease

4th The complete absence of supuration in any of the reported cases

5th The variation in the pathology, the finding of the earliest acute congestive stage along side of the last stages of destruction of nerve tissue and scar formation, indicating again a continuation of the virus and not the uniformity in pathology which is found in such disease as scarlet fever, typhoid, pneumonia, chicken-pox, small-pox, etc

Case History Patient, Mrs M B  
Age 30 years Seen on November 29, 1928

History given is that three weeks before she had had a bad head cold. This lasted a week or so, and she recovered without any treatment, and felt fairly well. On November 25, she again developed a cold beginning with a rhinitis, headache, ringing in the ears, felt chilly, and ached all over. By

the following day she had some fever and kept in bed, but did not improve.

She was seen by me on Thursday, November 29

At this time the patient had a temperature of 104, there was definitely present some congestion of the eyes and nose, throat was dry and glazed, and there was evidence of slight pulmonary infection, a few moist râles around the base of the lungs, posteriorly

The following day, she felt considerably better

On Saturday, also, she felt much better, but on Sunday she was seized with a very severe headache which became progressively more intense. Her temperature went to 101, and there was apparent some rigidity of the neck

She was taken to the St Vincent's Hospital

The findings at this time, on more complete examination, showed a marked rigidity of the neck, photophobia, slight ptosis of both eye-lids, generalized hyperesthesia particularly marked over the abdomen and legs. The abdominal reflexes were obtained with difficulty and disappeared a day or two later. There was a suspicious Babinski on the right side, and normal reflexes on the left

The leucocyte count varied between 8,000 and 11,200

On December 3 she was examined by Dr Chas R King for evidences of involvement of the sinuses, and the following report was made by Dr King

"In mydriasis. No blood vessel changes were noted. The media clear, no edema of the retina or disk. fundi

normal Ears, all landmarks present; no perforations, light reflexes of good quality Nose, frontal and maxillary sinuses clear to illumination Mucosa of the nose acutely inflamed, some mucoid material in the left middle meatus, origin undetermined No pus was seen in either nares"

An ex-ray of the head and sinuses was reported normal by Dr Murphy

On the third of December a spinal puncture was made Fluid was definitely under increased pressure, the cell count was 15 and globulin, a trace The patient's temperature, the day after admission, went up to  $102\frac{1}{2}$ , and ranged from 99 to  $102\frac{1}{2}$  for several days, finally dropped to 99.6, and did not rise above that during the balance of her stay in the hospital

She continued to be extremely sick The rigidity of the neck was constantly present, photophobia and ptosis were marked The hyperesthesia was particularly distressing to the patient, and a mild nausea was complained of She could take very little nourishment, as the effort of eating seemed to distress her She was dazed and was drowsy most of the time, but was easily awakened and responded to questions rather intelligently Some visual disturbances appeared, and she was unable to read the large headlines on the newspaper, and diplopia was complained of on two occasions

Under the usual treatment, including salicylates and glucose intravenously, the patient did not get any better

At this time it was impossible to make any definite diagnosis of gall-bladder involvement She was hyper-

esthetic and tender everywhere, and the tenderness was just as marked on the left side as under the right costal border, and had it not been for my previous experience with this problem, I should have found no excuse for further investigation of the biliary tract, but because of this experience and because she did not respond to any treatment but was definitely getting more and more drowsy and seemed to be suffering considerably, an attempt was made to pass the duodenal tube on December 10

This attempted drainage was not successful The tube was passed again the following day, and a very successful drainage was obtained of dark bile, rich in Gram positive cocci, and showing many epithelial cells both of the columnar and squamous type

The following day the patient showed very marked improvement The ptosis had disappeared, the rigidity of the neck was much less marked, and mentally she was perfectly clear, and she stated that she felt well enough to want to sit up in a chair

Drainages were repeated again on the 12th and 13th, with continued improvement, return of the abdominal reflexes, and disappearance of the Babinski on the right side

The clear-cut result in this case leaves little room for doubt in my mind and in the minds of the medical men around the St Vincent's Hospital who saw this case, that it can be attributed only to the biliary drainages instituted and the consequent lessening in biliary infection or toxemia

The microscopic findings in the duodenal contents removed by the tube

from cases of encephalitis have been quite variable. Many have been clear and without any remarkable microscopic picture. Usually the fluid is very dark and sticky. It changes very promptly, within a moment or two after removal from the bile tract, to greenish bile showing very early oxidation process.

Occasionally there are very large numbers of epithelial cells, squamous and columnar in type, with extraordinary numbers of Gram positive organisms, usually a coccus, very small in character, the cultural characteristics of which I have not worked out. Occasionally a very short, thin, Gram positive rod is noted in considerable numbers, and now and then the bile, as it comes out through the tube, is noted to be of an oily consistency. In other words, nothing characteristic is noted in the character of the fluid.

It is not my contention that the gallbladder shows any degree of infection. Rather do I feel that we are dealing with a toxic state, that whether bacterial infection was the primary cause of the condition or not, we are dealing either with the metabolic product of the bacteria in the gallbladder, or, more probably, with chemical changes in the bile itself, so that there is absorption of toxic products of a neurotrophic character into the circulation.

The possibility of an allergy, also, must be borne in mind in this type of condition. This possibility is somewhat heightened, too, by the occasional finding of a very marked improvement in the encephalitic condition, following the appearance of an extensive skin rash.

However, this subject needs considerable study before any definite conclusions can be drawn concerning it. Whether the condition be directly shown to be a toxemia or an allergy, the toxin or the sensitizing substance is probably located in the bile tract.

I do not mean to imply that all cases of encephalitis are associated with or caused by biliary tract pathology. We know that encephalitis occurs in a number of other conditions, such as various septic states.

I have reported, in the past, encephalitis following sinus infection, and dental infection, and have recently seen a very marked and very severe case following pelvic operation in which there was probably thrombosis of the pelvic veins. The fact that a similar type of encephalitis can occur in a number of conditions giving rise to toxemia also heightens the probability that the encephalitis following epidemics of influenza is of the same type, i.e., toxic.

My earlier experiences led me to feel that the majority of cases require surgical treatment. Experience with a larger number of cases requires revision of this statement. The majority respond well to non-surgical biliary drainage.

The indications for surgical treatment are

1st Failure to pass the duodenal tube, either because of lack of co-operation or comatose condition of the patient.

2nd Failure to get bile on two or three successive trials provided the tube is definitely in the duodenum.

3rd Conclusive evidence of cystic duct obstruction, i.e. failure to secure

"B" bile, or x-ray evidence of dysfunction of the gallbladder

Of my forty cases, fourteen were treated surgically. A larger series may show a still smaller percentage requiring radical treatment, especially if the condition is recognized early and proper treatment is instituted before the patient becomes too comatose to swallow the duodenal tube

It is certain that the experience reported here and in previous articles is worthy of the serious attention of the medical profession throughout the world in the hope that the observations reported by me may prove of real value in the treatment of this very serious and apparently hopeless disease

# The Histopathology of Appendiceal Amebiasis With Case Report\*

By WINSTON F. HARRISON, M.D., C.M., *Montreal, Canada*

THE case to be reported is of interest first of all because the patient had never been farther south than the State of Michigan. Secondly, the case presents some features rarely found even in districts where the disease is prevalent. Lastly, it is peculiar in the mode of diagnosis, which was made by study of the vermiform appendix in the course of the routine histopathological examination of material from the surgical clinic. Since the first reported case of amebic dysentery in the State of Michigan by Dock<sup>1</sup> in 1902 there have been from time to time reports which indicate that though the disease is not common it cannot be considered a great rarity in northern latitudes. The great majority of cases met with in temperate zones, however, give a history of having been in the tropics at some period of their lives. Symptoms of the disease have then appeared after a variable length of time, often after many years of residence away from tropical countries.

## CASE REPORT

N. K., a white male, age 40, a millwright by trade was admitted to the Medical Out-

patient Department of the University of Michigan Hospital, on July 31, 1928, complaining of ache and soreness in the abdomen. His present illness he dated to two years before, when he began to tire easily and to lose weight. Later, he had pain in the right lower abdomen coming on shortly after meals. For a time he had a "bloody diarrhea." The blood appeared after the bowel movement. He had suffered with piles for about 4 years. After the first attack the patient improved, but the symptoms recurred at intervals of 4 to 6 weeks. About two months before admission he began to have a constant soreness in the right upper abdomen. Two weeks later his local physician found a lump at the site of the soreness and made a diagnosis of hernia. The patient was advised to get a truss. The truss made the soreness worse. Since then he had had a steady ache in the right side. He began to lose appetite and to lose weight. He was unable to work because he felt weak and tired. The diarrhea had not been constant. At times he was slightly constipated. He had no nausea or vomiting, but had lately been much troubled with gas. He had lost 37 pounds in weight during the 13 months before admission. Three weeks before admission he noticed a swelling of the peri-anal tissue. Since this time he had some difficulty in defecation, and occasionally incontinence of feces followed by the passage of small amounts of fresh blood and yellowish material. He had never noticed tarry or clay colored stools.

*Past History* The patient had always lived in Michigan. His general health had been fair. He had measles and mumps in childhood. At the age of 2 years he had

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## Winston F. Harrison

an umbilical hernia, and at 9 a left inguinal hernia, but was not operated upon. He stated that he had had loose stools nearly all his life. From childhood until he was 18 or 19 years of age he had "ulcers of the bowel." No other relevant history was obtained at this time.

Family history was essentially negative.

Physical examination showed an emaciated male with good muscular and skeletal development lying comfortably in bed apparently without pain. The abdomen was slightly below the level of the thorax. Panniculus was scanty. The abdomen moved freely with respiration. Just below and to the right of the umbilicus a mass about the size of a turkey egg was felt. It had a definite border on the left and was nodular, firm and fixed. It was somewhat tender on palpation. Other parts of the abdomen were soft, and there was no splinting of the recti. The liver and spleen were not palpable. There were several tags of mucous membrane protruding from the anus. The rest of the examination was essentially negative.

While still attending the out-patient department he was referred to the Department of Surgery. The impression at this time was that he had a carcinoma of the cecum. He was admitted to the Medical Ward on August 16 where a more thorough examination was made. The X-ray findings were as follows: The first report stated that the appendix was visualized, movable and not tender at 24 hours and empty at 48, the cecum and colon were poorly filled with the barium meal, and had a smoothed out appearance. Later, a barium enema was given. The findings at this time are well shown in the accompanying plate (See fig 1). There was a definite obstruction to the flow of barium in the mid portion of the transverse colon. The cecum and ascending colon filled very poorly and showed irregularities of outline. A diagnosis was made of carcinoma of the colon in the region of the hepatic flexure. The chest plates showed no evidence of pulmonary disease.

The urine examination was essentially negative. The blood showed 4,440,000 reds,

9,350 whites and 60% hemoglobin. The stools (at this time 4 to 6 a day) were reddish brown, liquid, and showed considerable gross blood. There was a positive guaiac test. There were no other positive findings in 11 stool examinations. The patient's temperature ranged from normal to 99°, and the pulse from 80 to 90 during his two days on the Medical Ward.

A consultation was held with members of the Surgical staff. In view of the history and findings, and particularly the X-ray studies showing a very definite obstruction of the large bowel a provisional diagnosis of carcinoma of the colon was made. Operation was postponed a few days because the patient had a slight respiratory infection. On August 22 he was operated upon by Dr F A Collier under nitrous oxide anesthesia. A large mass was found involving the ascending colon, the hepatic flexure and part of the transverse colon. The bowel was injected, and the appearance was that of a massive inflammatory infiltration. The cecum and terminal ileum around the ileocecal valve were injected, thickened and indurated. Retroperitoneal lymphnodes were greatly enlarged. The appendix was remarkably thickened and infiltrated. The mass itself was too extensive to be removed. It was impossible to attempt an anastomosis or short circuit operation because of the condition of the large bowel which showed inflammatory thickening throughout its entire extent. Consequently an ileostomy was done. The appendix and small inflamed lymphnodes were removed.

A pathological examination was made of the appendix by Dr C V Weller in the course of the routine examination of material from the operating rooms. An ulcer in the wall of the appendix contained amebae. (The full report will be given below.) Regional lymphnodes showed a severe lymphadenitis.

In view of finding amebae in the appendix the patient's history was re-taken in part. He stated that he had had bloody diarrhea off and on since childhood. He thought he had piles. Two years before admission he was seized with a cramp in the right side, and had bloody diarrhea.

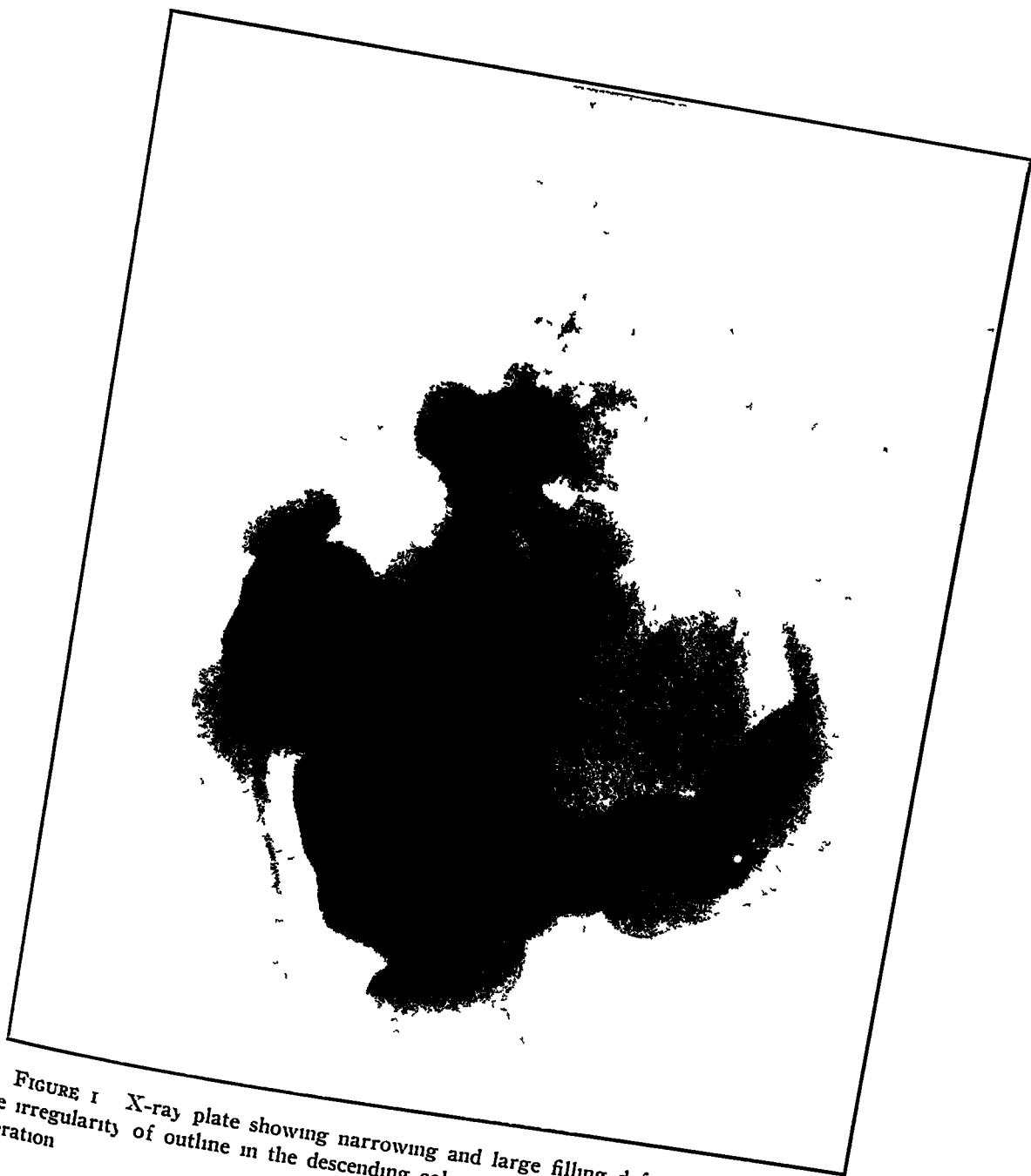


FIGURE 1 X-ray plate showing narrowing and large filling defect in the upper colon. The irregularity of outline in the descending colon is suspicious of the presence of amebic ulceration.



which persisted for 6 months. At that time he was associated with a man from Louisiana who had suffered with dysentery for 6 years. He drank out of the same cup, used the same toilet, but did not live at the same house. His diarrhea improved and he was fairly well until 4 months before admission, when the pain and diarrhea returned. Soon afterward he noticed a lump in the abdomen. After that time he became steadily worse. The patient stated that he had never been out of the State of Michigan except once, and that was to go to South Dakota for a short time.

Repeated examination of the whole stools finally revealed many amebae, actively motile. The type was *Entameba histolytica*.

Two days after operation the patient's condition became worse. The abdomen was distended and there were signs of consolidation at the base of the right lung. The following day, August 25, he died. Unfortunately an autopsy could not be obtained.

### DISCUSSION

It is not the intention to give here an account of amebic dysentery, but only to point out briefly some features of the present case and to give some account of the disease in the appendix.

Here then is a case which presented such prominent features of malignant disease that the real etiological factor was unsuspected until the pathological examination of the appendix gave the clew. Had the patient come under observation in a locality where amebic dysentery is prevalent the diagnosis would in all probability have been made earlier. The physician in the tropics comes to suspect amebiasis in cases presenting symptoms of intestinal disease until it can be ruled out. The malady is much less common with us. The Michigan Department of Health could give little informa-

tion as to its incidence because it is such an infrequent cause of death in this State that it is not classified separately. It was stated that cases are rare, and almost invariably imported from the south. Nevertheless within the past few years the number of cases seen in the Temperate Zone is steadily rising. Recently, Williamson, Kaplan and Geiger<sup>15</sup> made a survey of amebic dysentery in Chicago. They conclude that the disease is not uncommon in that city, and has frequently been overlooked. So it must be remembered that it is a cosmopolitan disease, and by no means confined to the tropics. At the time Hermann<sup>2</sup> (1919) reported two cases in this hospital there had been a recent collection of 500 cases in this country observed in a latitude corresponding to our own. The dissemination of the disease was much increased during the war by the movement of troops to and from tropical areas.

It is now well recognized that the *Entameba histolytica* is present in the large intestine of many people showing no symptoms of the disease. These amebae were found in the stools of 3% of all American troops, and 10% of those returning from France were similarly infected.<sup>3</sup> Dobell<sup>4</sup> says there is good evidence to show that from 7 to 10% of the population of Britain are infected with *E. histolytica*. Yet the number who show symptoms of the disease is very small. The same authority states that up to 1921 there were scarcely a dozen authentic cases of indigenous amebiasis reported in Great Britain. As far as is known the parasite is identical with that in the tropics. Just why it should

be so much more a tropical disease does not appear to be clearly understood. Not only does the incidence vary but the clinical manifestations are somewhat different. In countries away from the tropics the disease is more chronic. Boyers<sup>5</sup> says that the behavior of cases in the Temperate Zone suggests that the ameba meets with a number of adverse conditions that help to create a subtle picture of chronicity. He adds, "Whether this tendency to chronicity in large numbers of persons in the Temperate Zone means an actual relative immunity is not known." This individual had never been south of the State of Michigan. How did the patient become infected? A point in the history which was finally elicited suggests the answer. For some time previous to his severe attack two years before admission he was associated with a man from Louisiana who was known to have suffered from dysentery for 6 years. If we assume that the man from the south was a carrier it is not unlikely that the patient was infected through him. This would seem to be the most probable explanation in view of his previous good health, unless we are to take into account the somewhat vague history of loose stools and "ulcers of the bowel" in childhood. Man can become infected with *E. histolytica* in only one way, and that is to swallow the cysts of the organism. Authorities believe that the carrier is the biggest factor in the transmission of the disease, and that contaminated water supply plays a small rôle if any. The cysts are ingested by the accidental contamination of food or drink

by minute particles of feces containing them.

In the present case it is interesting to note the things which pointed to intestinal malignancy. First, there was the history of the presence of a lump in the abdomen appearing gradually, diarrhea, and at times constipation, with bloody stools, indigestion, loss of appetite, progressive loss of weight and strength. This, together with the finding of a palpable firm mass, the irregular filling defect shown in the x-ray plate, blood and mucus in the stools, the presence of anemia with only slight leucocytosis, and practically no elevation of temperature. At operation the surgeon considered that the tumor mass together with other parts of the large bowel and the retroperitoneal tissues had the characteristics of a massive inflammatory infiltration rather than those of neoplasm. It is important to note that the terminal ileum at the ileocecal valve was also involved.

This type of lesion in intestinal amebiasis is apparently very uncommon. In 1925 Runyan and Herrick<sup>6</sup> working in the Panama Canal Zone reported 4 cases very similar to this showing "amebic tumors." They state that the condition had not until that time been reported in the literature on amebic dysentery. They describe this type as a massive ulceration due to a chronic amebic infection causing enormous thickening of the wall of the bowel. The condition affects the upper large intestine, principally the cecum, and also, as was shown in all four of their cases, the terminal ileum. The first two were tentatively diagnosed tumor of the kidney and

carcinoma of the cecum respectively, while the last two, "as the result of increasing experience" were correctly diagnosed. In a paper on x-ray diagnosis of intestinal amebiasis Dr J J Vallarino<sup>7</sup> describes the roentgenological findings in one of the four cases. The infiltration had almost entirely closed the lumen of the transverse colon. The patient had every indication of a severe and rapidly growing intestinal malignancy. Whether in the present case the narrowing of the lumen of the bowel was entirely due to infiltration or if there were also strictures from contraction of the gut is not certain in the absence of anatomical evidence. Each condition is reported to occur, though very rarely in the course of chronic intestinal amebiasis.

In the literature on amebic dysentery the vermiform appendix appears to have been singularly neglected by most writers. Councilman and Lafleur<sup>8</sup> in their classical monograph, while giving detailed reports of autopsied cases did not mention the appendix. Most text-books of Pathology either fail to mention it or say that it may be involved, though rarely. Sandwith,<sup>9</sup> in his Lettsonian Lectures (1914) on amebiasis speaks of affection of the appendix only once, stating it to be a very rare complication. Several authorities, however, particularly in recent years, have shown how frequently the organ is involved and its importance especially in surgical amebiasis, and also its relation to the question of carriers and re-infection. Harris<sup>10</sup> in 1898 was the first to report a case of amebic appendicitis although Kartulis, working in Egypt

years before, had mentioned finding amebae in smears of contents of the appendix removed post mortem. Schaudinn (1903) who classified the parasites and identified *Entameba histolytica* as pathogenic for man found amebic appendicitis in rabbits in the course of his experiments. Rogers,<sup>11</sup> after much experience with the disease in India concluded that the appendix is often severely affected by the amebae, and instanced cases of fatal peritonitis following perforation. The most extensive work in recent years appears to be that by James<sup>12</sup> and his associates and by Clark,<sup>13</sup> all working in the Panama Canal Zone. They give some prominence to the incidence of appendiceal amebiasis. Clark found that in 186 cases at autopsy 76 had amebic ulcerative appendicitis and 9% had either perforation or abscess formation. He considers that owing to the structure of the organ and that fact that the lumen tends to become more or less obliterated in adult life it may readily become a "carrier pocket" and difficult to treat successfully. These authorities and others now remove the appendix in some instances where medical treatment has been unsatisfactory. Last year Coates and Groves<sup>14</sup> in England, coming to the same conclusions reported 3 such cases very successfully treated by operation.

Cole and Heideman have recently reported a case of amebic ulcer of the abdominal wall following appendectomy with drainage. They found amebae in the ulcer, but although "unusual bodies" were found in the wall of the appendix they were unable to demonstrate the presence of parasites here,

and thus to prove the starting point of the lesion on the skin surface. In their conclusions these writers intimate the "possibility that amebas may influence the pathologic process in the appendix in some cases of appendicitis." This is no longer a matter of doubt. There are abundant references in the literature showing that the parasites themselves are sometimes responsible for lesions in this organ, and that amebic appendicitis is a well recognized condition.

We now turn to the pathological findings in the present case.

#### **PATHOLOGY OF APPENDIX**

##### *Gross pathology*

The appendix is of normal length, but averages about twice the normal thickness. Toward the tip the wall is thinned over a dilated lumen containing a soft material. The surface is roughened by adhesions and by a small amount of fibrinous exudate. On cutting across the appendix the lumen is found to be somewhat dilated throughout the entire length, and markedly dilated in the distal third. Mucopurulent material escapes from the cut lumen. There is no evidence of neoplasm.

##### *Microscopic pathology*

The appendix was examined by microscopical sections cut at 3 levels representing the junction of the quarter segments of the organ. The most distal section shows a very marked dilatation of the lumen with a small amount of mucopurulent exudate still remaining. This has apparently been the site of a fecal concretion since there is a marked pressure atrophy

and chronic catarrh of the mucosa. The wall shows fibrosis, with mononuclear and polynuclear infiltration including many eosinophiles. The subserosa shows a marked fibrosis with mononuclear infiltrations and numerous peritoneal adhesions.

Microscopic sections taken from the mid point of the appendix show a moderately dilated lumen. There is a marked chronic catarrh of the mucosa and the same evidences of a chronic appendicitis as found in the section first examined. At this level the serous surface shows a small amount of unorganized fibrinous exudate. Interrupting the mucosa at one point there is an ulcer which extends to the inner circular fibres of the muscularis propria. The greater part of this ulcer lies in the lymphoid tissue of the submucosa. It is bordered in part by a very slight amount of vascular granulation tissue, but for the greater part by the structural elements of the appendix itself. The neighboring tissues are infiltrated to some distance in each direction with polymorphonuclear leucocytes. The ulcer shows an overhanging mucosal edge surrounding its ragged undermined margin. Its base is covered with fresh purulent exudate in which there are numerous amebae to be described later.

The most proximal section from the appendix shows a dilated lumen surrounded by a greatly thickened wall. The general tissue changes are the same as previously described although the purulent infiltration in the wall is somewhat more extensive and there is more fibrin on the peritoneum. About one-fifth of the mucosal surface is the

site of an ulcer (See fig 2) This ulcer extends slightly into the circular portion of the muscularis propria, is slightly concave at its base following the contour of the circular muscle, and at its border undermines the mucosa leaving an overhanging, inwardly rolled shelf of mucous membrane (See fig 3) The ulcer is much larger than the one seen in the preceding section, and at its base there is a leucocytic infiltration extending practically through the appendix wall. The base is covered with fresh and old pus, fragments of necrotic tissue and partially hemolyzed blood clot. Scattered through this material there are numerous amebae, but the parasites are especially numerous in the lower part, the exudate adjacent, or in contact with the living tissue.

#### *The amebae*

In the fixed and stained preparations the amebae average about 60 microns in diameter. In shape they are roughly spherical with a slight blunt lobation. Many show an irregularly crescentic narrow zone or more lightly staining and less granular ectoplasm about the main mass of cytoplasm. The endoplasm stains a medium purplish blue with hemalum and eosin and contains numerous irregular granules, fragments of ingested nuclei, many vacuoles, and in most instances red blood cells in various stages of hemolysis (See figs 4 and 5) The nucleus is in most cases excentric in position and is about 10 to 12 microns in diameter.

It varies in staining from red violet to purplish blue, in most instances taking the eosin to a sufficient extent to give it a reddish coloration. Toward the periphery of the nucleus, deep blue to bluish black chromatin material can be seen in small crescent-shaped masses in some cases. From these characteristics, particularly the very general ingestion of red blood cells and the presence of these organisms in an ulcerative lesion, recognition of this ameba as *Entameba histolytica* (*Loeschia coli*) seems to be fully justified.

#### SUMMARY

1 A new case of chronic amebic dysentery is reported in a man who had never been south of the State of Michigan.

2 The case showed such features of malignant disease that a tentative diagnosis of carcinoma of the colon was made. The diagnosis of amebic dysentery was made during the routine examination of the appendix following operation, on the pathology of the ulcers and the finding of the amebae.

3 Appendiceal amebiasis is not an uncommon complication of the disease. It is now considered to be important as a "reservoir" in chronic cases and in carriers. Appendectomy has been successful in cases not responding well to medical treatment.

4 A description is given of the histopathology of the appendix in this case.

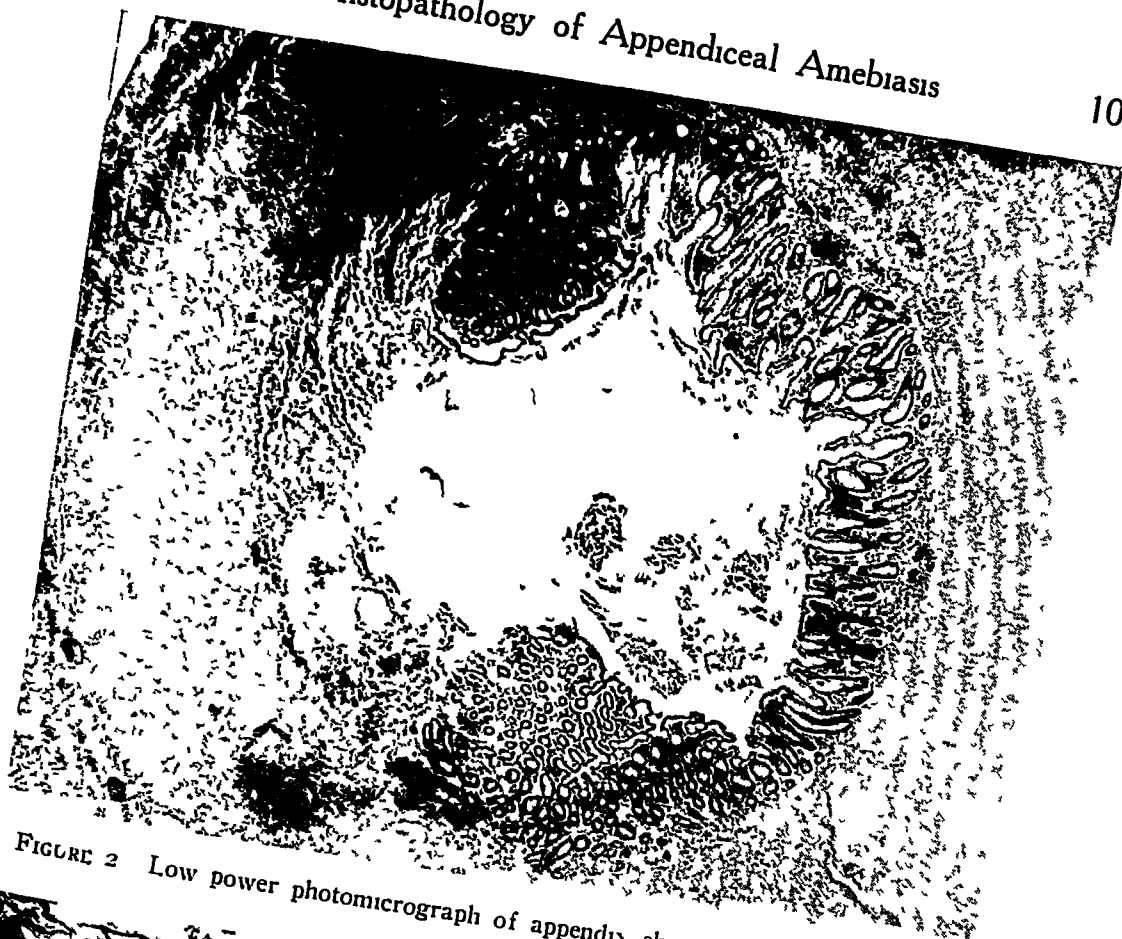


FIGURE 2 Low power photomicrograph of appendix showing large amebic ulcer

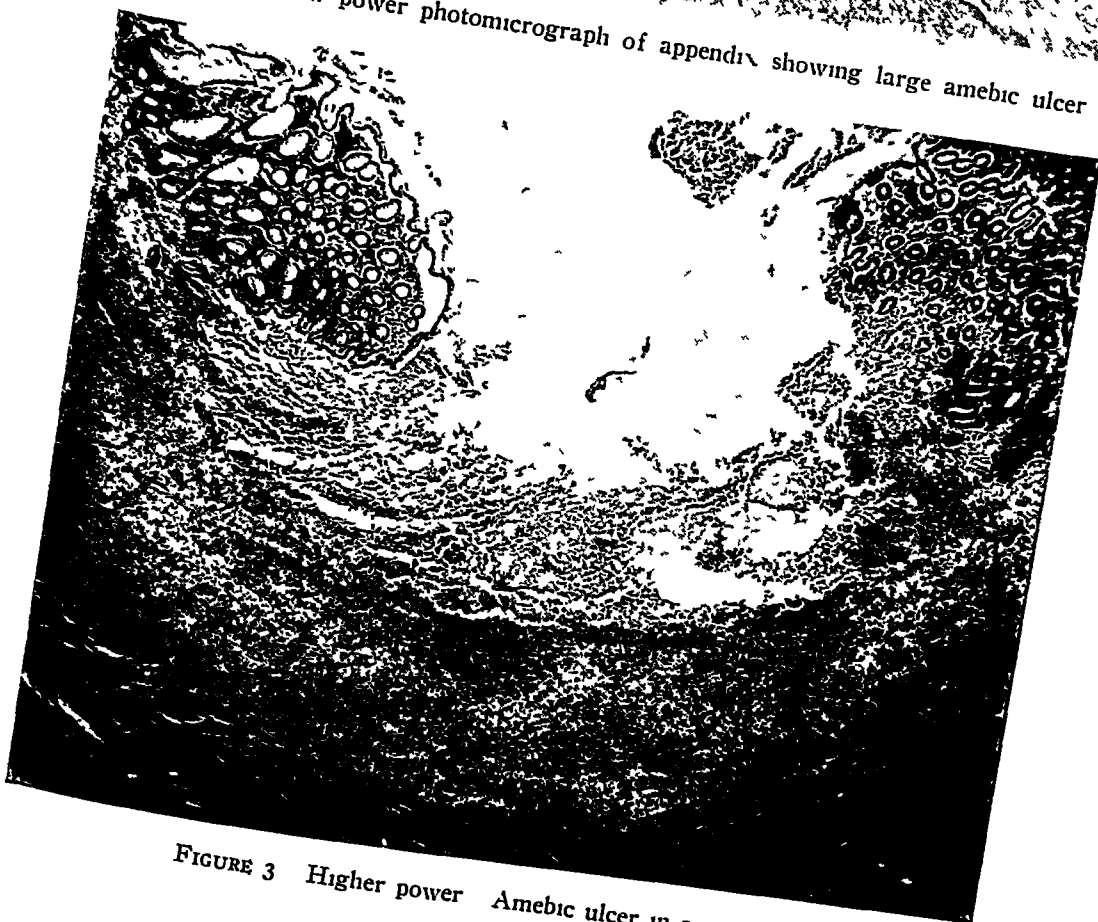


FIGURE 3 Higher power Amebic ulcer in appendix

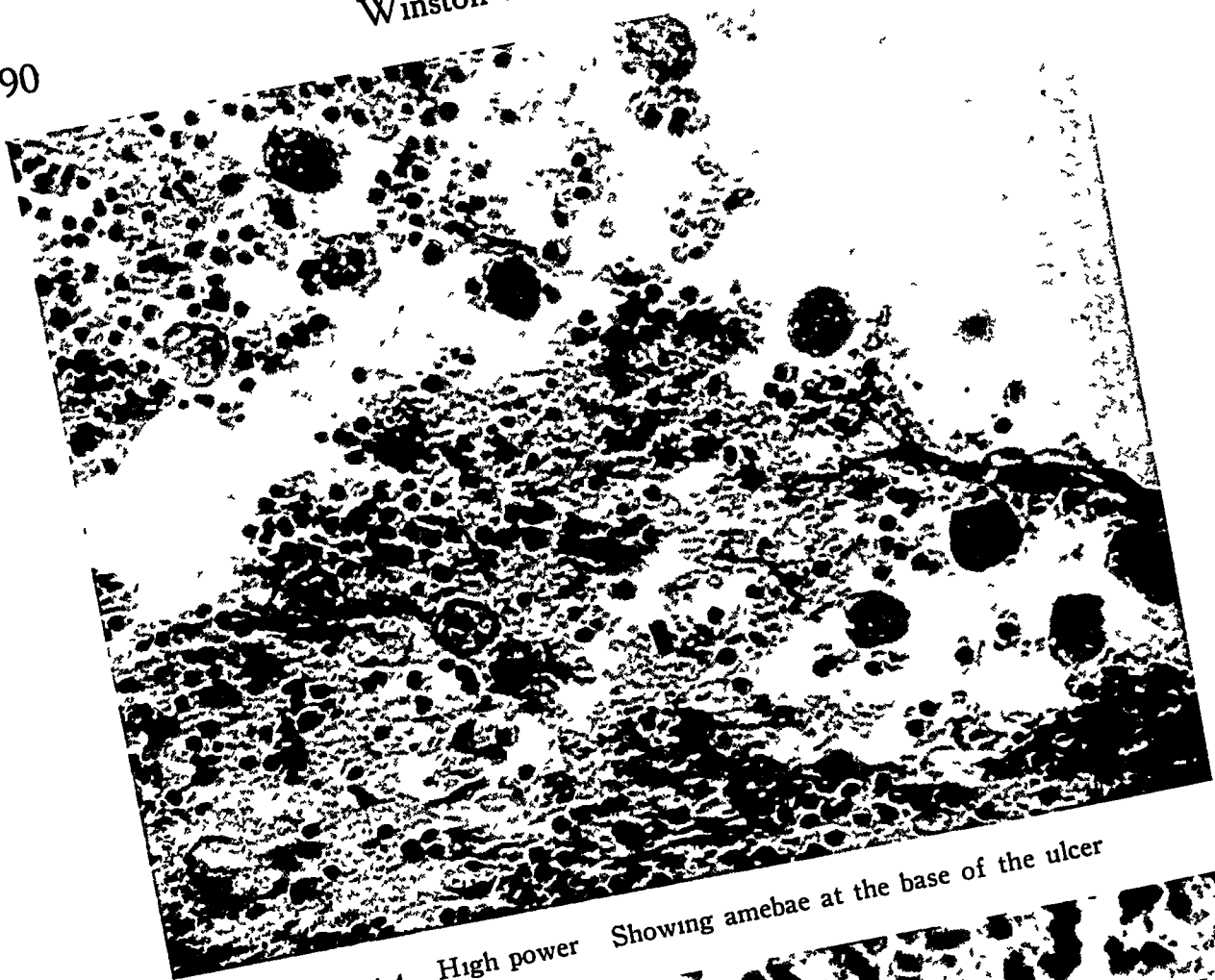


FIGURE 4 High power Showing amebae at the base of the ulcer

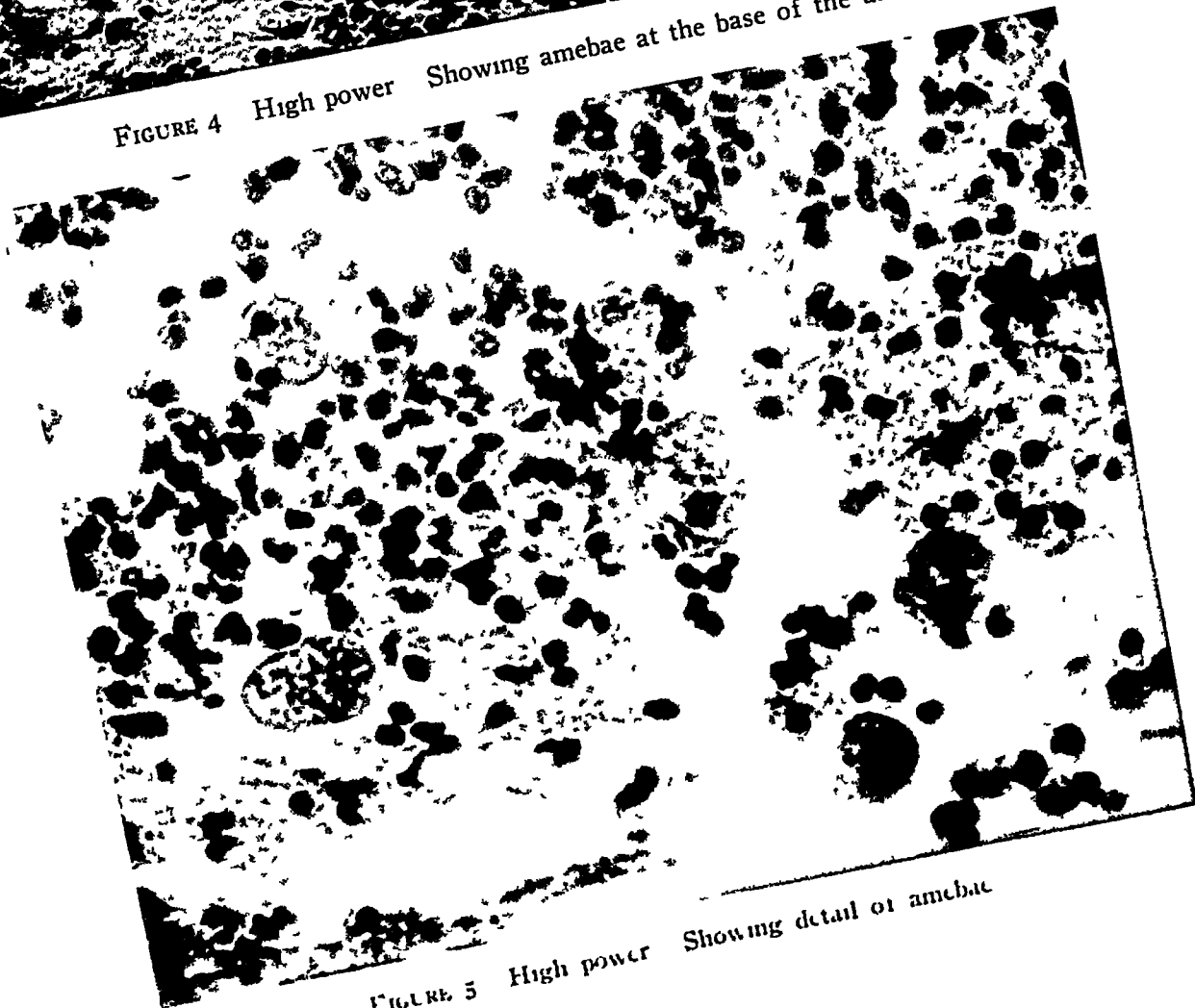


FIGURE 5 High power Showing detail of amebae

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# Tularemia\*

A Consideration Based on a Resume of the Literature and Personally Observed Cases with a Report of an Unusual Complication.

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## INTRODUCTORY

SEVERAL interesting features attach to this relatively new disease in man. So far, its incidence has been confined to the United States and Japan, and while it would seem reasonable to expect it to be found wherever certain rodents exist, it has not been recognized elsewhere outside of our country. Second, it was discovered in the course of a general study of diseased rodents. Third, it occurs in nature as a highly fatal disease of certain animals, while recovery is the rule in man. Fourth, within one year after the disease was recognized, the causative organism was identified. Fifth, both were discovered by the same investigators. Sixth, its identification and early study is to be credited to the Public Health Service. Seventh, notwithstanding its relative infrequency in man it possesses high developmental capacity when accidentally inoculated. Eighth, the evolution of our present knowledge has been wrought by trained workers in special fields—a public health worker

discovered the disease in animals, a clinician recognized and described the first human cases, a serologist found the antibodies in his own blood and a bacteriologist recovered the organism from an ocular infection in man. Ninth, the organism was named from the county where the diseased animals were first found. Tenth, despite the short period between its recognition as a separate disease and the discovery of its cause and despite the prompt publication of the results of studies, ten years elapsed before the rodent disease in California and Utah deer fly fever in man were recognized as the same disease, though both were studied in the same year—1911.

It was called Tularemia by Francis and may be described as a specific plague-like infectious disease occurring in nature in certain rodents with occasional transmission to man in a milder form and is due to the *Bacterium tularense*.

It was originally found in the Western states by McCoy and Chapin in 1911. Since that time it has been found occurring in every section of this country except New England, Wisconsin and Washington and singularly has not, as yet, been found out-

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side of the United States except in Japan

*Mode of Transmission* McCoy, in 1911 published a description of a disease found among ground squirrels in California. The disease was discovered during a systematic examination of rodents carried on at the Federal Laboratory, San Francisco. He demonstrated the transmissibility of the disease to mice, rabbits, gophers, guinea pigs and monkeys, but failed to isolate any organism from the plague-like lesions so produced. The next year he and Chapin isolated the specific germ and were able to grow cultures on egg-yolk medium. By this discovery a new disease was established, the organism was named *Bacterium tularense*, from the county of Tulare and the disease has come to be recognized in the literature as Tularemia. Cases of infection in man began to be recognized. Chapin became a victim of accidental laboratory infection. The six laboratory workers connected with the public health investigation from 1920 to 1927, likewise contracted it. Similar laboratory infections have been reported notably by Ledingham and Fraser. The Lister Institute of Preventive Medicine, London, exhibiting a high degree of scientific curiosity procured a culture of *Bacterium tularense* from the Hygienic Laboratory, Washington, D. C., with which they infected guinea pigs. Three of the workers fell victims to the disease, their ardor cooled and the experiments were discontinued. The spontaneous development of the disease in man began to be noted and recorded until now, it has been recognized in every section of the U. S.

Insects play an important rôle in the transmission of the disease. The deer fly, the wood tick, the mouse louse, the stable fly and squirrel flea have been shown capable of such transmission in the laboratory. Game birds, as in the case of the grouse, apparently have been carriers. Handling infected animals has been the usual method of infection, the bacterium finding entrance through an old or fresh wound on the hands. More disturbing than the tick and fly transmission or direct inoculation, is the possibility of transmission by undercooked meat of infected animals as indicated by Freese. Another possibility is by inhalation when laboratory workers handle animals with extensive pulmonary involvement as seems to be established by Parker and Spencer. The same authors have demonstrated that the germ can be transmitted by such intermediate hosts as the wood tick, the eggs, nymphs and larvae may carry the specific bacterium from the parent. If this holds true under conditions outside the laboratory, it becomes at once apparent that when a species of insects become infected, the number of such infected insects may assume tremendously greater proportions than if infection of adult insects occurred only by feeding on diseased animals.

Inoculation from man to man has not been reported and Francis thinks this does not occur. If this method of transmission did obtain, it would be expected that doctors would have been almost certain to have become infected, especially during the earlier period when the disease was not generally recognized, and would now

come to light Harris has reported a case, however, that indicates the possibility of contact infection of nurse or physician. A mother while dressing the initial ulcer and a wound resulting from incising a necrotic gland on a child, infected her own hand, the skin of which was injured by a safety pin and was followed by a typical glandular type of the disease. While all of the cases seen by me have been traced to infections from dressing rabbits, I can see no reason why injuries to the skin received while dressing human ulcers or wounds following incision of necrotic glands may not become portals of entrance of the specific bacterium.

No instances of infection, by natural means, in domestic rabbits grown in hatches have been reported. Artificial infection can, of course, be established. The wild cotton tail rabbits, snow shoe rabbits and jack rabbits, have all been found infected in nature. The rabbit tick and the rabbit louse are the usual means of transmission in the rabbit family, and, fortunately, neither of these insects bites man. The various blood sucking fly families and the wood tick are the usual carriers from animals to man. Another source of transmission has been added to the list of rodents already known to be carriers of the disease, through Perry's report of the discovery of naturally infected field mice in California. Field or meadow mice are often infected by mites. These mice live in nests and migrate for food and it appears probable that tularemia is transmitted among them by the mites. The bacterium has been demonstrated to be capable of sur-

viving the winter in the tick and may be transmitted in this insect from generation to generation. The bed bug, not to be outdone by the louse, has joined the ranks of possible carriers. Since the squirrel flea carries the disease from ground squirrel to ground squirrel, it is not unreasonable to suppose the *pulex irritans* may vie with his cousin and increase man's likelihood for infection.

It is one of the most transmissible diseases in laboratory experience. Chapin's accidental inoculation in 1911 might not be considered as unexpected but the number of laboratory workers since 1919 that have been infected can be explained only on the basis of high transmissibility. They were all trained laboratory people and in addition, knew the great risk, hence, took unusual precaution to protect themselves. When these facts are borne in mind, one ceases to wonder why handling or dressing rabbits results in human infection but rather why more are not so infected.

Of forty-nine human cases studied by Francis, fourteen were inoculated by flies, one by ticks, ten had dressed jack rabbits, ten had dressed cotton-tail rabbits and fourteen were laboratory workers who had necropsied infected laboratory animals. That twenty-eight and five-tenths per cent (28.5%) of the total cases Francis tabulated should have been inoculated in scientific investigation constitutes an amazing testimony of the danger of this disease to the laboratory workers.

The Public Health Service has emphasized the tick, fly and dressing wild rabbits as the more frequent sources

of infection. From a seasonal standpoint, the importance of each of these will vary in different localities, hence the disease may be termed endemic, for it may be found somewhere in the United States alone in practically every month during the year.

*Pathology.* Only four cases of tularemia in man have been studied at necropsy up to November 1927. The first was reported by Veibye in 1924, the autopsy being done by Sellinger. This case died eighteen days after the onset of illness and eight days following an exploratory laparotomy. The diagnosis was made after the laparotomy but before death by the agglutination test and cultures from inoculated guinea pigs, rabbits and mice done after the necropsy. Nodules ranging in size from a shot to a walnut were found in the lungs. The spleen was soft, the pulp being almost semifluid in consistency. Circumscribed yellowish white nodules were scattered throughout its substance and definite areas of necrosis with increase in fibrous tissue was found.

The second case died and a partial necropsy exposing only the spleen and liver was done in 1919, the case being reported by Francis in 1927.

The third case was studied by Bruecken and was a complete autopsy with exhaustive study by fixed tissues, stained sections, cultures of heart blood and animal inoculations in 1926 and was reported by Francis in 1927. Circumscribed nodules were found which were both caseous and fibrous. The spleen was dark in color, quite soft and contained caseous nodules. The supra-renals contained opaque,

yellow and grayish translucent areas. Lymph nodes were enlarged and showed yellow foci. The lungs contained enlarged peribronchial lymph nodes as well as old calcareous areas and fibrous tubercles. Enlarged lymph nodes were found in the omentum and near the ileo-cecal valve. The urine contained albumin, casts and pus cells. Cultures from blood obtained from the heart showed only streptococcus hemolyticus. Biopsy study of the lymph nodes found an increase in connective tissue fibers which contained nodules whose walls were made up of epithelioid cells interspersed with fibroblasts and the usual inflammatory reaction. Findings, the centers were necrotic, the blood vessel walls showed proliferating endothelial cells, a marked edema of the walls and reticulum increase.

The fourth case with the most complete pathologic study yet made was reported by W. Simpson from Dayton, Ohio. This was the most rapidly fatal case on record (four days, seven hours). The autopsy findings consisted of multiple focal necrosis in epitrochlear and axillary nodes, and in spleen, liver and right lung.

In a study of pathological histology found in diseased animals by Strong and Councilman, they found miliary foci in the lymph nodes, liver and spleen of guinea pig which consisted of mononuclear cell accumulation, infiltration with polymorphonuclear leukocytes and necrotic areas. Necrotic areas were also found in the liver but no capillary lesion. Similar lesions were found in the adrenals, heart and lungs. There was also a general infection of the blood vessels, endothelial cells and the bacteria were

found in the vessels in all parts of the body. In the adrenal glands the cortical cells were the structures chiefly involved. The kidneys were infected throughout the glomerular structure and accumulation of mononuclear cells were found. They consider that the essential lesion is an infection of the endothelial cells, most marked in the blood vessels of such organs as the spleen and liver. They found staining of the bacterium in the tissues was difficult, though diagnosis could be definitely made in this way. Hemorrhagic areas in the lungs and kidneys were common.

The changes occurring in the vascular system take on the nature of an obliterative endarteritis most commonly. In the early lesions of the tissues, large numbers of histiocytes were uniformly present. In all the lesions of the cases which have been studied post mortem, the findings were sufficiently identical to be explained only on the basis of a common pathogenesis. As would be experienced in the pathological study of laboratory animals, those which are most highly susceptible show a more diffuse affection of structures. The white mouse has been found to lend the most ready demonstrations of the bacterium in smears and sections as well as in cultivating organisms from the blood. The lesions in the human show a rather marked contrast from those of susceptible animals, in that in the former, fibrous tissue proliferative cell changes are the most characteristic. This is explained on the basis of higher resistance and a degree of immunity. In the study of lesions in man, the similarity of appearance of tular-

emic changes to those incident to tuberculosis has often been emphasized. This confusion has been made more probable because *Bacterium tularensis* has not as yet been stained in sections from human lesions.

*Immunity* Only one case of a second infection in man has been found in my study of the literature. This was reported by Lake and Francis and developed in a technician in the Hygienic Laboratory at Washington and developed two and one-half years after the first attack. It developed as a papule on the finger, was followed by lymphadenitis of the arm, presented no constitutional symptoms and the bacterium tularensis was isolated by inoculation of a guinea pig. Since the agglutinins persist for many years in the blood of persons recovering from the disease the infrequency of second infections is easily understood. This degree of immunity appears not to obtain in susceptible animals, a circumstance not yet explained.

*Diagnosis* It is frequently stated that tularemia is a new disease. I think it would be more accurate to state that it is a newly recognized disease. From 1924 to 1926, the reported cases ran from fifteen to three hundred and twenty-three and the recthirty-four states. Up to May 1, 1928, 613 cases have come to the notice of Francis. Who believes that these changes in figures were the result of an actual increase in geographic distribution? Many observing physicians who now are recognizing tularemia are also recognizing identical cases seen before the time of its clinical identification but which they called

something else then. The rodents now recognized as the "reservoirs of infection," a phrase of Francis and Calender, have not made the United States their recent habitation. Rabbits and ground squirrels are indigenous. Neither have flies, fleas and ticks come to torment them only with the advent of 1911.

Another evidence of the truth of this conviction was introduced by the establishment of the identity of "Ohara's Disease" with tularemia. Ohara studied an acute febrile disease in man contracted from handling wild rabbits in Japan. A number of cases fell under his personal observation and were rather carefully studied. He concluded that there was a causative relationship between the handling of uncooked rabbits and the illness of his patients. He further concluded that eating the cooked meat did not transmit the disease. The symptoms described in his cases were sufficiently identical with those recognized as tularemia in this country that further laboratory study including agglutination test of patients was carried out. Blood serum from seven of his cases were sent to the Hygienic Laboratory U. S. Public Health Service during the years of 1925 and 1926, they all agglutinated *Bacterium tularensis*. Inoculation of guinea pigs was also done at the laboratory from human lymph glands removed from Dr. Ohara's patient and the cultures obtained were identical morphologically and culturally with those studies obtained from this country. Animals inoculated with this culture died presenting the usual typical lesion of tularemia and the pathological study

of the glands of these animals corresponded with the pathological findings of cases studied originating in the United States. Francis and Moore concluded that Ohara's Disease was identical with tularemia.

*Laboratory.* Agglutination of *Bacterium tularensis* is considered equally dependable, diagnostically, as isolation of the organism. Francis says, "I know of no other disease in which an agglutination test will set the diagnosis right in such uncertain terms after so many years."

The serum of the blood from the suspected case is obtained in the same way as serum for a typhoid agglutination test and is performed in a similar manner to the well known Widal. The blood should be obtained under sterile conditions and no antiseptic should be added. If the specimen is to be transported over a distance to the laboratory, pure glycerine may be added to the serum in equal amounts.

Agglutinins develop in the blood of the patient by the twelfth to fourteenth day of the disease. The degree of development may reach a dilution of 1:1200 or even more. The blood reaches a maximum agglutinin titer by the fourth or fifth week followed usually, by a gradual decline, though in one Lister Institute case the maximum was still noted at the end of 403 days. The agglutinin property lasts, probably, through life. The longest period of persistence was reported by Brosius where a case now thought to have had tularemia infection in 1909 was found by Francis to agglutinate *Bacterium tularensis* in January 1928.

The germ is small, round or rod-shaped, 0.3 to 0.7 micron in length, 0.2 to 0.3 micron in width and is often capsulated. It stains poorly with methylene blue but fairly satisfactorily with carbol-fuchsin or gentian violet or Giemsa's solution. They are found in many organs of the body and in the blood. Pus from the initial ulcer, a suppurating gland or the ophthalmic secretions should be ground in a mortar, suspended in normal saline, strained and injected subcutaneously into the abdomen of a rabbit or guinea pig. If tularensis bacterium is present, the animal should, within two weeks, show at post mortem, caseation of the inguinal glands and multiple foci of necrotic areas in various organs, particularly the liver and spleen.

Cultures may be obtained from the blood, liver or spleen of these animals. The media most satisfactory for culture growth are egg yolk and serum glucose cystin agar. No growth occurs on plain agar. A diagnosis from smears or culture inoculations cannot

be made. The gross pathology found in the inoculated animal is of much more value diagnostically. Injection into rabbits or guinea pigs of blood from severe cases in man results in infection and death, a fact which establishes the bacteremic nature of the disease. Attempts to cultivate the organism from the blood of human cases have failed in most of the cases. Francis was able to recover it in two very severe cases. How long the germ lives after drying and exposure to air or sunshine has not been determined but it remains virulent for at least a month in spleens or livers of animals that have died from the infection, if placed in glycerine and kept in the ice box.

*Clinical* In man the disease appears chiefly as a glandular and a typhoidal type. In the ulceroglandular form the initial sore can usually be demonstrated. It takes on the nature of an ulcer (Fig 1), sluggish in its appearance and process of development and healing (Fig 2). They rarely attain great size, one to two

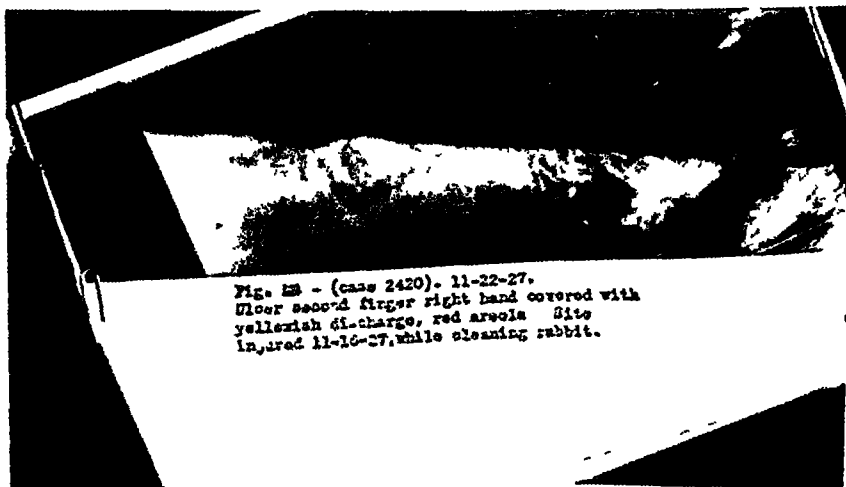


Fig. 1 - (case 2420). 11-22-27.  
Ulcer second finger right hand covered with  
yellowish discharge, red areola. Site  
injured 11-16-27, while cleaning rabbit.

FIG 1

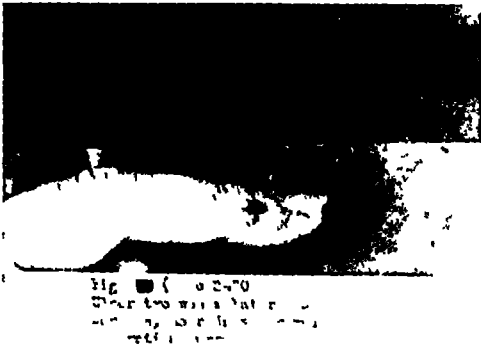


FIG II

cm being the average diameter, are shallow, rather clearly defined with little or no redness or infiltration of surrounding tissue. They are superficial, 0.1 to 0.2 cm deep and the surface is covered with a grayish membrane not easily removed, hence but little discharge. The ulcer is rarely multiple (Fig 6), but multiplicity seems to have no effect on the degree of severity of the other symptoms. It is usually painful but never assumes the degree of discomfort which usually accompanies an ordinary septic wound. The glands located in the drainage area generally swell, varying widely in size, are firm, fairly fixed and frequently become necrotic and require removal or drainage. The overlying skin may become reddened resembling the usual streptococci infection and the lymphatic vessels may become involved presenting a brawny feel to the examining finger. Usually the adenitis is confined to the extremity presenting the initial lesion but enlargement of the cervical glands and those of the opposite side of the body often occur. The glands may suppurate but this has not been common in our series. Those not sup-

purating may remain enlarged for several months.

I see no reason for not including the ophthalmo-glandular group of cases under the heading, ulceroglandular type. Here the primary lesion is on the conjunctivae instead of the skin and constitutes the initial lesion which is both external and demonstrable. Conjunctival cultures are positive in such cases. The incubation period is short—three to five days being the average, two days is the shortest period and ten being the longest in the reported cases studied. The symptoms occur rather abruptly and consist of chilliness, myalgia, headache, prostration and fever. Pain is usually experienced in the swollen lymph glands within forty-eight hours after the prodromal symptoms and twenty-four hours before attention is attracted to the local lesion. The latter begins as a papule, rapidly necroses and is characterized by its sluggishness, three or four weeks often being required for healing.

The temperature ranges from 99 to 104, more frequently the maximum does not exceed 102. It is irregular in curve, resembling the course of a septic case and reaches normal in from two to three weeks (Fig 3).

The blood picture is not characteristic. Leucocytosis of moderate degree occurs, if a high count appears it should suggest a mixed infection. The stained cell study affords no diagnostic help.

Judging from the post mortem findings in the liver of animals dying from natural or inoculated infections, one would expect jaundice as a rather frequent symptom. Veibjycke reported a



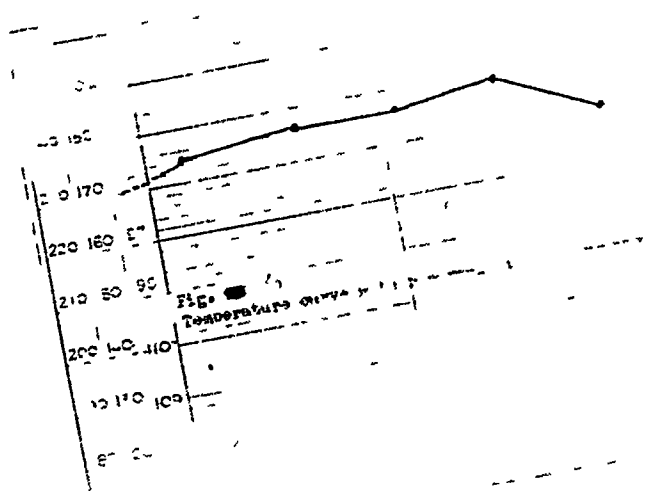


FIG III

case with icterus which was subsequently necropsied. An additional feature of interest in this case was the sequence of events as learned by Francis in his study of the case, two days after dressing rabbits, the patient injured her right index finger with a splinter, the disease developing three days later. Fulmer reported a series of eighteen cases from Arkansas in which there was one death. This patient died on the twelfth day of illness with what was diagnosed as general peritonitis. No other cases of peritoneal involvement have been found to be recorded.

The other type resembles typhoid fever and runs a similar temperature range (100-104), but the remissions are usually accompanied by free perspiration. In this respect it resembles so-called septic conditions. Chills, likewise, are not uncommon in this type just as they occur in the ulceroglandular type. Prostration is quite marked even from the onset, persisting after the fever has passed. While the definite febrile period may be a

bit shorter than in typhoid, complete convalescence is tardier, the keen desire for food and rapid gain in weight, rather the rule in typhoid, is absent in tularemia of the typhoid type. Another differential feature, clinically, is the absence of the rather frequent complications such as intestinal hemorrhage during the febrile period and phlebitis in the convalescing period. While the majority of the cases of typhoid type do not present glandular enlargements, it does occur. Two of the three cases developing in the Lister Institute had some gland involvement. The symptoms of such cases as do not show glandular enlargement are materially identical with the ulceroglandular type with the sole exception of the primary ulcer and the gland swelling. In fact, the closer one studies the symptoms of one's own and reported cases, the more the conviction grows that they are, after all, tularemia, that symptoms in either type are merely suggestive and a diagnosis must rest on the serum reaction, and that a better classification

would be *tularemia with primary lesion and gland involvement* and *tularemia without demonstrable primary lesion and gland involvement*. Most of the reported cases of typhoid type have been in the person of laboratory workers. Kavanaugh's case was a housewife with a history of having handled a rabbit from which her daughter-in-law contracted the ulceroglandular type of the disease, the blood serum of this case agglutinated bacterium *tularensis* in dilutions from 1:10 to 1:160 and terminated fatally.

No satisfactory explanation has yet been offered concerning the means of entrance of the germ in these non-ulcerative, non-glandular cases. Conveyance of the infection from the hands to the mouth to be swallowed must be considered a possibility. Whether the germ may be inhaled as occurs with the tubercle bacillus is considered as a possibility when one has seen the post mortem pulmonary lesions in animals. Francis suggests the possibility of the entrance through unbroken skin surfaces because of the presence of cystin in the skin and the known cystin requirement in media for the organisms' growth. Just why a papule should not be formed when the organism is absorbed through unbroken skin and yet colonize in a broken area with ulcer formation and gland involvement is not clear.

Walter Simpson has reported a fatal case of only one hundred and three hours duration and quotes a letter from Francis relating three cases in one family of short duration, death occurring on the 6th, 8th and 9th days respectively. The occurrence of 49 cases in his series observed in Day-

ton in four months would seem to indicate a more common incidence of the disease than hitherto appeared. He was able to trace twenty-five additional cases occurring prior to 1927 dating back to 1908. On the other hand, in the county of Harlan, Kentucky, where this paper was read, a country where ticks and wild rabbits abound, no cases had been recognized by more than twenty-five physicians present.

Convalescence in the man is the rule, indeed death may be said to be rare. Recovery is, however, very slow, three or four months after the infection may still find the patient a semi-invalid, but when it does occur it appears to be complete. I have seen no deaths but three months incapacity was observed in one case and five in another. This latter case merits some detail.

Case 3140-S. A farmer, age 37, was seen in consultation with Dr. Rush, Fern Creek, Kentucky, December 8, 1925. He was first seen by Dr. Rush about November 7, 1925, on account of an infected finger caused by a table fork while eating a rabbit which he had just cleaned. He was put to bed and one week later began to have pain in the precordial region and dyspnea. He ran a temperature from 101 to 103, perspired freely and had profuse night sweats. There was some cough and a blood-tinged sputum was observed for several days. There was marked prostration. He had enjoyed lifelong good health and his family history was negative except for one brother who had died of pulmonary tuberculosis.

Examination, physically, showed a well developed and well nourished man with the appearance of being acutely ill, respiration was labored, feeble respiratory sounds and a modified percussion note were noted over the lower lobe of the left lung, outer half, posteriorly, while over the inner half ex-

## Virgil E Simpson

tending two inches from the spine was an area of flatness and bronchial breathing. The apex beat was indistinct but the point of greatest intensity was inside the dull area. A friction rub was heard to left of sternum over the fourth intercostal space and scattered moist râles over the left lung root. Capillary circulation fair and an increased cervical pulsation was noted.

Blood pressure	105
Systolic	62
Diastolic	86
Heart Rate	83
Pulse Pressure	43
Mean Pressure	69%
Heart Load	

The ulcer on the right index finger was two cm in diameter, with irregular edges, filled with a purulent discharge and surrounded by a narrow zone of redness and induration. The olecranon and axillary lymph nodes were enlarged, firm, movable and tender on the right side, while on the left side the axillary glands were enlarged but smaller.

Blood Count	5,440,000
Red Cells	10,350
White Cells	90%
Hemoglobin	86
Color Index	72%
Stained Specimen	7%
Polys	19%
Mono L	2%
Mono S	
Eosin	

Urinalysis	Straw color
Appearance	Acid
Reaction	1023
Sp Gr	Trace
Albumin	0
Sugar	0
Acetone	0
Diacetic	0
Indican	
Microscopic	
Occasional Red Blood Cell	
Urates	
Occasional hyaline cast	

12-9-25

## X-Ray Study of the Chest

Fluoroscopic examination of the chest shows a greatly dilated cardiac shadow, the left margin of the heart comes within one inch of the left lateral chest wall. The dilatation to the right side is three inches to the right of the spine. The aortic and great blood vessel shadows do not appear increased in size. After the patient's head had been elevated fifteen degrees, there was no apparent change in the contour of the cardiac shadow. No examination was made in the erect posture.

On the antero-posterior film, made at a 36 inch distance in the supine position shows the cardiac shadow as revealed in fluoroscopic examination. The transverse measurement at the base is ten inches. There is a general mottling of both lung fields which is probably due to passive congestion. It appears to be very symmetrical in outline and appears to involve all portions of the lungs (Fig 4)

12-10-25

Urinalysis	Acid
Reaction	1022
Sp Gr	3 plus
Albumin	0 25%
Sugar	0
Acetone	0
Diacetic	Trace
Indican	
Microscopic	
Squamous & Renal Epith Cells	
Red Blood Cells, many	
Oxalate calcium crystals, few	
Occasional granular and hyaline cast	

Aspiration of pericardial fluid was done for diagnostic reasons, and 30 cc of fluid removed.

## Laboratory Examination

Straw colored  
Slightly cloudy  
Red Blood cells few  
Lymphocytes many  
Short rod shaped bacilli  
Few streptococci  
Temperature chart, graphic  
Fig 5



FIG IV Case No 3140-s X-ray of chest, antero-posterior, 36 inches, Recumbent

Blood serum agglutinated bacterium tularensis to 1-60 dilutions

The wound of index finger slowly healed  
Smears from pus showed staphylococci and streptococci

Discharge from Hospital on own request, improved, January 6, 1926

On March 11, 1926, he was again examined, looks fairly well Valve sounds negative Apex beat inside mammary line Heart regular and rhythmic

Blood pressure

S	132	P P	122
D	112	M P	20
H R	85 sitting	H L	26%
	144 erect		

Lungs clear Lymph glands in right axilla still large, firm, movable and tender Submaxillary gland on right side enlarged, not tender

Blood Count	
Hemoglobin	85%
Red Cells	4,560,000
White Cells	8,300
Polys	69%

Lymphs L	7%
Lymphs S	20%
Eosin	2%
Baso	2%
Urinalysis	
Reaction	Acid
Sp Gr	1030
Albumin	0
Sugar	0
Acetone	0
Diacetic	0
Bile	0

Microscopic

Occasional pus cell

Urates

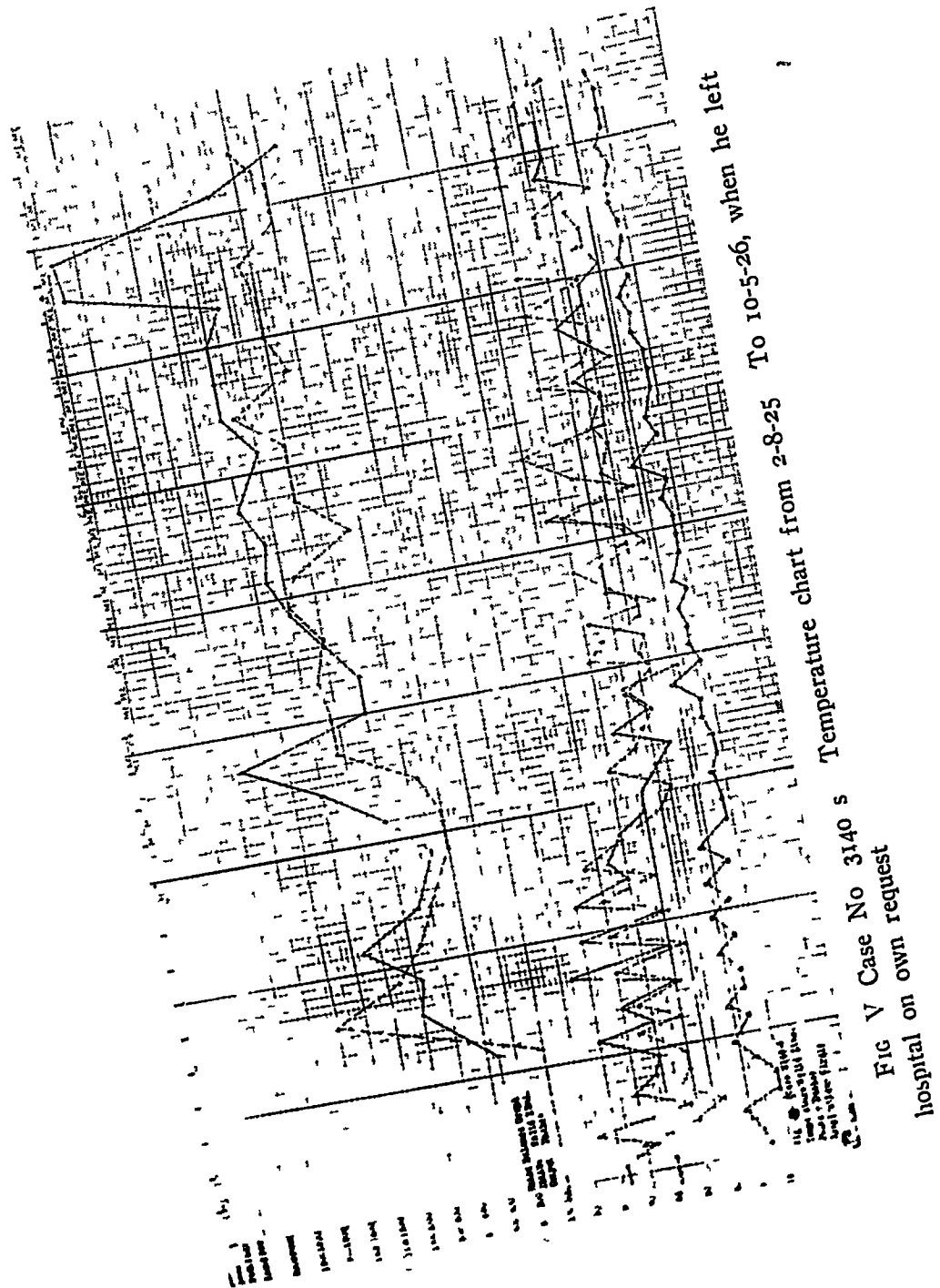
10-18-26

Weight 190 lbs

Heart rate 84, Valve sounds negative  
Chest clear No friction rub Complained some discomfort on exercise in precordial region

Case 2826 Is reported because of two features—multiple ulcers and absence of lymph node enlargement

Female age 43, was seen on account of ulcerating wounds on the thumb and little finger of the right hand and moderate pros-



tration The ulcers were small and showed but little discharge (Fig 6) The glands of the right arm and axillary space were apparently normal in size and not tender The temperature was normal and remained so at time of each visit (Fig 7)

Polys	62%
Small Lymphs	29%
Large Lymphs	9%
Eosin	0
Baso	0

12-5-27  
 Blood Count  
 White Cells 7,400  
 Hemoglobin 85%

12-7-27  
 White Cells 9,600  
 12-22-27  
 White Cells 11,000

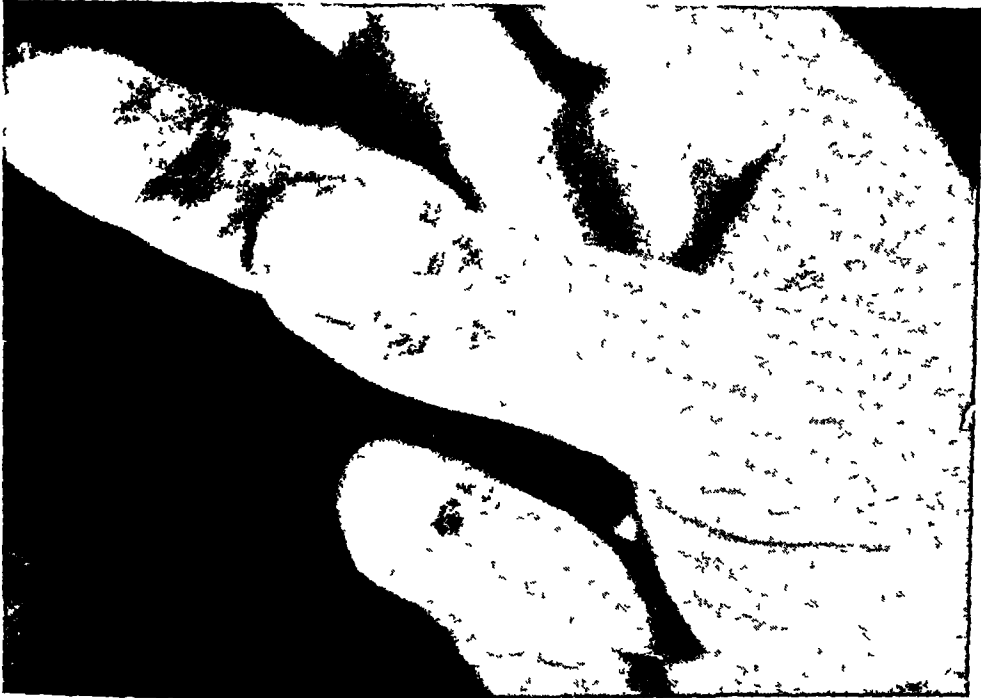


FIG VI Case 2826 multiple ulcers, photographed ten days after development

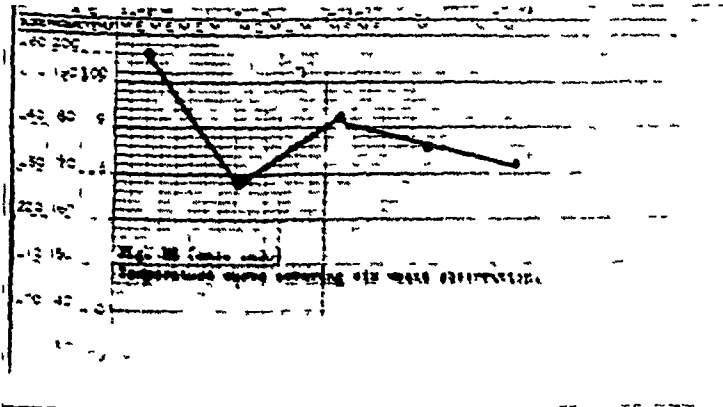


FIG. VII Temperature Curve, same case, from 12-2-27-to-1-10-28

1-25-28

White Cells	9,500
Hemoglobin	75%
Polys	44%
Small Lymphs	48%
Large Lymphs	3%
Eosin	1%
Mononuclears	4%

Blood serum agglutinated bacterium tularensis in dilutions 1-180

*Summary* The unusual evolution of our present knowledge of the disease is traced

Attention is called to the high degree of transmissibility of the disease to laboratory workers and the relative rarity of the disease through ordinary modes of transmission

The high fatality to animals con-

tracting the disease either through inoculation or by natural means and the low incidence of death in man is stressed

It is suggested that the nomenclature be changed

Tularemia with initial lesion and glandular involvement and tularemia without demonstrable initial lesion and glandular involvement being considered more comprehensive than the present classification

The rarity of man to man inoculation is considered

The apparent life-long immunity of the disease in recovered cases in man is emphasized

A case with pericardial effusion with recovery is reported

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## Editorial

### MARCELLO MALPIGHI

1628-1694

It was a rather striking and interesting coincidence that the anniversaries of three men to whom we owe so much of our knowledge concerning the vascular system should have been celebrated in 1928. William Harvey's great masterpiece "*De Motu Cordis et Sanguinis*" was published in 1628 at Frankfort by an obscure German publisher, Wilhelm Fitzer, in the same year Marcello Malpighi was born on a little farm at Crevalcuore near Bologna, and in 1728 John Hunter came into the world at the village of Long Calderwood, Lanarkshire. Truly three of the greatest in the history of medical science, to whom the medical and scientific world paid due honors in 1928! It was especially fitting that Malpighi's anniversary should have been celebrated at the same time with that of Harvey, for it was he, who in his first published work in 1661, supplied the missing link in Harvey's chain of investigations—that of the capillary circulation. And this was made possible through Malpighi's use of the microscope which Harvey did not possess and consequently could not see the capillaries. It has been well said that Malpighi made a histologic certainty of what Harvey had made a logical necessity. About 1650 there began to be constructed and employed in scientific investigations

crude microscopes employing simple lenses of high power, and with such instruments many of the most important discoveries of the second half of the seventeenth century were made. With such a lens Malpighi saw for the first time the capillaries in the lung of the frog. Luck was with him in his selection of an organ for this research, because of the transparency of the frog's lung and its relatively conspicuous capillaries. At any rate he saw them and recognized their function for he describes in the 1st edition of his work "*De Pulmonibus*," Bologna, 1661, the passage of blood from the arteries to the veins through the "capillary" blood vessels. Harvey had only inferred their existence, Malpighi demonstrated it. In a figure in this work the capillary network of the wall of the pulmonary sac is clearly indicated, as is also the vesicular nature of the lung tissue. He also saw a similar capillary network in the wall of the frog's distended urinary bladder. This important discovery was recognized by the Royal Society of London, and it was republished at Leyden and in other places in the years following. This discovery may well be considered the beginning of microscopic anatomy, and Malpighi may be considered its founder, so important were the discoveries made by him with his simple microscope. He applied it to the

study of both animal and vegetable structure. At a very early period he concerned himself with the study of plant histology in anticipation of the more difficult investigations on the histology of animal tissues. He had knowledge of the spinal vessels of plants as early as 1662, but it was not until 1671 that he wrote his *Anatome plantarum*. This he sent to the Royal Society, who published it in the next year. Just a few months before its publication there had been brought out in London under the title of the "Anatomy of Vegetables" an English work, by Nehemiah Grew, which clouded considerably Malpighi's priority as a plant histologist. However, his priority in animal histology along so many important lines is so incontestable that the question of his priority in plant histology becomes a matter of very secondary importance. In the *Anatome plantarum* there was included an appendix, "*Observations de ovo incubato*" which described the development of the chick, particularly the later stages, surpassing in many points of detail the work of Harvey along the same line. Unfortunately he developed the metaphysical conception of preformation in the undeveloped ovum in connection with his objective observations, to the impairment of the value of the latter. Harvey's work on "*Exercitationes de Generatione Animalium*" had appeared in 1651, twenty years before Malpighi, applying his microscope, was able to describe in detail the development of the organs of the embryo, particularly of the heart and nervous system. He thus laid the foundations of microscopic embryology. But the researches

of Malpighi on the structure of the brain, liver, spleen and kidneys were perhaps of as great importance as his discovery of the capillaries, equally epoch-making in character. In an epistle addressed to his old fellow student, Fracassato, *De cerebro exercitatio epistolica*, he showed that microscopically the white matter consisted of round but flattened little fibers arranged in bundles forming tracts connecting the surface of the brain with various regions of the spinal cord, further he showed that the gray matter is not confined to the surface of the brain where it is called cortex, but exists in scattered masses in the interior, disposed around the ventricles and along the cord. In this epistle he was unwilling to define exactly the nature of the gray matter, but later, influenced by his work on glands, he came to the conclusion that it was of a glandular nature, describing the superficial gray matter as "glands hanging on to the strands of the white fibers like the fruit of the date palm." At the same time he was working on the tongue and skin, discovering in the latter the lower layer of the epidermis which we still call after him the rete Malpighi layer. In 1666 he published the results of his investigations on the glandular organs under the title of *De viscerum structura exercitatio anatomica*. He cleared up the mystery which had so long hung over the liver by showing that it was constructed after the fashion of a conglomerate secreting gland, that its substance was arranged in small masses essentially like those of which other conglomerate glands such as the pancreas and salivary glands

were made up, and to these he gave the name of *acini*. He regarded the common duct as the excretory duct of the liver, the liver secreting bile as the salivary glands secreted saliva. He did not pretend to answer the questions by "what mechanism is the bile separated in the glandular acini of the liver and what is the use of bile in the economy," but expressed himself as "contented to have described the simple and rude structure of the liver." Nevertheless Malpighi's description of the microscopical structure of the liver remained with little change up to the present century. Similarly Malpighi came to a clear conception of the microscopic structure of the kidney. He showed that in man the kidney was really made up of several kidneys consisting of masses of tubules arranged in the form of pyramids, since known as the pyramids of Malpighi. He showed that the tubules constituting these pyramids ended in orifices at the summit of the papilla which formed the apex of the pyramid, and further that in the cortex of the kidney the tubules were not straight but irregularly twisted. He showed further that these tubules begin as inflated swellings or capsules, "round like the eggs of fishes," containing a knot of blood vessels, hung on to the small arteries as "apples hang on to the branches of a tree." The Malpighian tufts or corpuscles we have called them ever since. Malpighi was convinced that they played an important part in the secretion of urine. Practically our knowledge of the kidney structure remained where Malpighi left it until the time of Bowman. Finally the nature of

the structure of the spleen was revealed through Malpighi's observations. He gave a thorough description of its capsule, trabeculae, pulp, blood vessels and nerves, showing it to be not a gland but a contractile vascular organ. He was the first to observe the small white bodies, not unlike glands, attached to the blood vessels, which ever since have been known as the Malpighian corpuscles. During the remainder of his life Malpighi continued to work on anatomical and physiological problems and wrote important tracts on the uterus, hairs, hoins, bone, cardiac polypi, the lymphatic glands, anatomy of plants, natural history of the silk-worm, but none of these attained results equal to the epoch-making investigations already mentioned. His writings on the nature and causes of disease justify for him the credit of being regarded as having laid the foundations of scientific pathology. Malpighi's name stands out as the fore-runner of modern medical science. He represents the beginning of a new epoch, that of the microscope. He is truly the father of microscopic histology and embryology. It has been said of him that he left his mark upon whatever branch of natural history he touched. He may be called a zoologist, a structural botanist, a comparative anatomist, an embryologist, histologist, pathologist, physiologist or biologist. He stands out as the first researcher who comprehended the essential identity of plant and animal life. Upon every problem that he touched he shed light. Malpighi's personality has been described as most attractive; he was gentle, patient, fair-minded, sensitive

and sympathetic, and a devoted practitioner of medicine. In study he was accurate and untiring, exceedingly bright and quick of comprehension, and moved to the depths of his being by a passion for the new learning. He was delicate in constitution and subject to frequent illness. His life was uneventful, and without romance. He was honored throughout the world and beloved at home, he had many scientific friends and correspondents, but peaceful in disposition as he was, his long life was made unhappy from time to time by attacks made upon him by a neighboring family with whom there existed a life-long feud arising out of disputes over property boundaries. He was most happily married but was childless. He entered the University of Bologna in 1645 as a student in philosophy, but as the result of the deaths of his father and mother, family cares, and the aforementioned feud, his studies were interrupted until 1651, when he again definitely took up his studies with the intention of studying medicine. In 1653 he became a Doctor in Medicine and Philosophy, and after three years of medical practice was made a Professor in Medicine. In the same year there was created for him a new special chair of Theoretical Medicine at the University of Pisa which he held for three years, teaching and experimenting. Because of domestic difficulties in Bologna, and the unfavorable climate of Pisa he resigned his chair there and returned to Bologna where he spent the next four years in teaching, practice and research, developing the ideas that later were to come to such splendid fruition. In

1662 he was offered the chief chair of Medicine in the University of Messina which he held for four years. Pressed to remain longer he asked permission to make a visit to his native city. Received most warmly in Bologna as a token of the great fame his researches had already brought him, he was offered the Chair of Medicine in his home city. Released by the Senate of Messina, much against their desire, Malpighi once again took a chair in his old University, which he held for a quarter of a century, lecturing, practising medicine and giving the best energies of his mind to his investigations. In 1667 his connection with the Royal Society of London was begun, which led to a long and close intercourse between Malpighi and the English Society. As a result of this the Royal Society had the honor of publishing the greater part of Malpighi's works which he produced after his return to Bologna. The years passed uneventfully, he spent his winters in the city busy with teaching and practice, his summers in the country in rest and research. The loss of many of his manuscripts through a fire in his house in Bologna in 1684 left him much broken, and the old family feud continued to harass him, almost to his last days. In 1691, Pope Innocent XII invited him to come to Rome as the Pope's physician. At first refusing, Malpighi was at last unwillingly made to accept the invitation. Soon after his arrival there he became ill, had a slight apoplectic stroke in 1694, and another more severe a few months later from which he died on the 29th of November,

## Editorials

1694 Thus passed a very great man, the kidney and the Malpighian follicles of the spleen. Would that every the one who most truly marks the beginning of modern medicine. His medical student as he comes into contact with this name might be inspired name is eponymically preserved for us to read these epoch-making works in the rete Malpighi, the pyramids of Malpighi, the Malpighian capsules of which these terms commemorate!

## Abstracts

*Heat Stroke a Thermoregulatory Incompetency* By EBEN E. SMITH, Lt Commander, Medical Corps, U S N (U S N Med Bull, Vol 26, No 5, 1928)

The present discussion is concerned with those phenomena resulting from failure of a normal individual to maintain normal physiology under influences favorable to heat accumulation. Smith draws the following conclusions. Heat stroke is a thermoregulatory incompetency resulting from exposure to heat. The clinical manifestations of heat stroke are of several types, but these various conditions have a common pathogenesis. Thermoregulatory failure may occur through cardiovascular collapse before hyperthermia develops. Hyperthermia develops through failure to dissipate heat. It results from an unbalance of reaction between complex physical and physiological factors. Profound acute metabolic disturbances occur in heat stroke. The trauma resulting from heat stroke affects parenchymatous tissue and may cause a fatal morphological disorganization. Tetany is an important element in heat stroke. It commonly affects the heart and may cause sudden death. It also affects smooth muscle and may prevent water assimilation through intestinal spasm. Heat, per se, is not the cause of the tissue trauma. The response to heat exposure develops toxic factors when thermoregulation fails. The nature of these factors is hypothetical and undetermined. Loss of water and salt is a significant fact in that it is a very important element in causing thermoregulatory failure and cramps. It probably also seriously embarrasses metabolic processes. An uncompensated acidosis occurs in heat stroke. This, as yet, can be attributed to no single acid body, and the condition probably results from the accumulation of the various acid products of metabolism. An acute interstitial pneumonitis occurs. It is of sufficient degree to

decrease materially the vital capacity and retard respiratory exchange. Summing up our known knowledge of the condition of thermoregulatory failure, heat, accelerated metabolism, depletion of tissue fluid, decreased respiratory exchange, increased hydrogen concentration, and parenchymatous degeneration represent the sequence of essential events in the pathogenesis of heat stroke.

*Effects of Communicable Diseases on Thyroid Gland* By ROBERT OLESEN, Surgeon, United States Public Health Service (Public Health Reports, November 16, 1928, No 46)

Infections and intoxications have long been believed to constitute etiological factors in the production of goiter. Many English observers, notably McGarrison, have relegated iodine to a minor etiological rôle. He considers goiter to be an infectious water-borne disease, the exciting cause of which is an organism belonging to the colon group. Crotti also strongly supports the infectious origin of simple goiter, holding that it is due to an organism of the trypanosoma type. Most Americans regard simple goiter as a deficiency disease. Investigations by Olesen and Taylor among school children in Cincinnati, Ohio, and the State of Connecticut failed to show any relationship between diseased tonsils and decayed teeth and simple goiter. Studies by Hertzler and Bram likewise failed to establish such a connection. The present article treats first of the thyroid status of 589 boys and 636 girls who were examined before and after they had had certain communicable diseases. In the accompanying control group the thyroids of 1842 boys and 1783 girls who did not have communicable diseases during the interval were examined one year apart. After the illness no changes in thyroid size were detectable in 51.7 per cent of the boys and 45.6 per cent of the girls. Thyroid

## Abstracts

size was diminished in 138 per cent of the boys and 11 per cent of the girls. Increased size was noted among 345 per cent of the boys and 434 per cent of the girls. The thyroid of 1842 boys and 1783 girls who did not have communicable illness in the interval were examined one year apart. No change in thyroid size had taken place among 484 per cent of the boys and 436 per cent of the girls. Thyroid size had decreased in 127 per cent of the boys and 186 per cent of the girls, while an increase was recorded among 388 per cent of the boys and 357 per cent of the girls. A communicable disease census of 7,977 boys and 8,441 girls showed little difference in percentage incidence among the thyroid-normal and the thyroid-enlarged children who had the same maladies. There is some evidence to show that one of the immediate effects of communicable diseases among girls of elementary school age is a simple enlargement of the thyroid gland. However, this thyroid enlargement appears to be temporary in character. A comparatively short time, the length of which is as yet undetermined, after a child recovers from a communicable disease, he is no more prone to changes in thyroid size than a child who has not had a communicable disease. In so far as elementary school children are concerned, there appears to be no ground for assuming that the ordinary communicable diseases are responsible for goiter. The underlying causes of this malady must be sought for in other directions.

*Liver Diet and Tar Cancer* By J. Maisin and A. FRANCOIS (Annales de Médecine, Paris, 24, 1928, p 345)

Two groups of mice were employed for this investigation, controls, which were fed with wheat flour, corn and white bread, and the second group that received in addition to this same diet, 5 gm of fresh liver three times weekly. All of the mice of both groups were painted with tar three times a week for 120 days. On the one hundredth and twentieth day cancer was observed in 215 per cent of the mice kept on the liver diet, but only 416 per cent of the controls fed with liver developed cancer. Of the two hundredth and twentieth

day cancer was observed in all mice fed on the liver diet, but only 6286 per cent of the controls had developed cancer. The percentages of pulmonary and axillary metastases were 379 and 594 respectively in the controls, but were 55 and 726 in the liver-fed mice. The control mice lived seventy days longer on the average than did the mice fed with liver. The same results were obtained when dried and ether washed powdered liver was substituted for the fresh liver in the diet. These results appeared to the investigators as highly significant, they explain the situation by the assumption that the liver acts in these cases, not simply by increasing the protein content of the diet, but by means of some specific substance similar to that acting upon the bone-marrow in pernicious anemia. If these experiments of Maisin and François can be confirmed and prove to be constant results of liver feeding in the production of tar-cancer, it will prove to be a discovery of first class importance in cancer research.

*Die Wirkung des Insulins auf die Lipochromemie und die Xanthosis Diabetica* By A. WL. ELMER and M. SCHEPS (Klinische Wochenschr., February 12, 1929, p 300)

The previous investigations concerning xanthosis diabetica have not considered the effects of insulin upon the lipochromemia and its clinical changes. Elmer and Scheps have had recent opportunity of studying five cases of xanthosis diabetica, and the effect of insulin upon the lipochromemia and the skin coloration. These observations showed that the lipochromemia is dependent upon the nature of the food given to the diabetic, such as eggs, spinach, carrots, etc., that are rich in lipochrome, and that xanthosis diabetica appears in some cases shortly after such a diet is initiated, and slowly retrogresses when such lipochrome-rich diet is stopped. This retrogression of the xanthosis takes place more quickly when insulin is given than when it is not used. When a lipochrome-rich diet is used insulin cannot prevent the formation of xanthosis diabetica, yet it acts so that the lipochromemia does not reach such a high degree as it would in the absence of insulin, and the

skin coloration is correspondingly less. In three other cases in which xanthosis diabetica had appeared after a lipochrome-rich diet, it was possibly by the use of insulin to lessen the degree of skin coloration, but without restricting the lipochrome diet neither the appearance of xanthosis could be prevented nor its disappearance be brought about. These observers further showed that insulin affected the alimentary lipochromemia in diabetic cases without xanthosis. They conclude that insulin has an influence upon the lipochrome metabolism, in cases of xanthosis diabetica it produced a lowering of the lipochromemia, and prevents often the appearance of the skin coloration, or at least reduces it greatly. It increase the action of a lipochrome-free diet in that it hastens the disappearance of the xanthosis. In the diet-resistant cases of xanthosis diabetica it is recommended that insulin be used in aid of the lipochrome-poor diet. Insulin alone, without the help of such a diet, can in many cases not prevent the appearance of xanthosis diabetica. The significance of the action of insulin upon the lipochrome metabolism is very interesting, in that it would appear to indicate that in xanthosis diabetica the nutritive factor is not alone concerned, but that also a disturbance of lipochrome metabolism plays an important rôle.

*Beiträge zur Lehre von den angeborenen Herzfehlern*. By W. RÖDISCH and H. RÖSLER (Wiener Arch f. innere Med., 1929, Bd. VXi, p. 463).

Rosler has been engaged in the study of congenital heart lesions for the last three

years. He has shown that the analysis of the röntgen findings has advanced essentially the differential diagnosis of these cases, much more than was to be expected from the existing literature upon the subject. Further, the study of his cases showed that consanguinity was an etiological factor of great importance, and perhaps alcohol. In continuing the systematic study of these cases the capillary microscope has been used, and the present paper deals with its application to the study of congenital heart lesions. Thirty-six cases were investigated by this means, in these particular attention was paid to the appearance of cyanosis, particularly of distal parts, to drumstick fingers and toes, and the corresponding capillary picture in the limbus of the finger- and toe-nails. For the purposes of comparison a second series of acquired heart disease of various kinds, nine cases in all, was studied. As a result of this study the authors conclude that there is a characteristic capillary picture for severe congenital lesions of the morbus coeruleus type. This capillary picture is dependent upon a capillary dilatation which is regarded as the cause of the morbus coeruleus. There is no connection between the capillary dilatation and the development of drumstick fingers. In isthmus stenosis of the aorta the capillary picture is characterized by numerous capillary aneurysms, and by the delicacy and smallness of the capillaries of the toes in contrast to the capillaries of the upper extremities. This finding occurred in the two cases of stenosis of the aorta examined, and was absent in all of the other forty-four cases studied.



## Reviews

*Recent Advances in Bacteriology and the Study of the Infections* By J HENRY DIBLE, M B (Glasgow), M R C P Professor of Pathology and Bacteriology in the Welsh National School, Late Professor of Pathology in the University of London 363 pages, 22 illustrations B Blakiston's Son & Co, Philadelphia, 1929 Price in cloth \$3 50

This is an attempt by a general student and reader of medical bacteriology to present in a readable form some of the more recent changes in the subject and to indicate the lines upon which it is evolving. It has been the author's endeavor to take a broad view of many subjects, and, in keeping the balance between extreme technicality and what is already common knowledge, to present a readable exposition of recent work which the general medical reader may appreciate. At the same time the author seeks to indicate to those who do possess some knowledge of bacteriology and the infections what is being done in spheres outside of their own. The rapid evolution of the subject makes it impossible to take notice of all of the most recent work. The period covered is, therefore, roughly that from the commencement of the War to the beginning of 1928. The writer has, perforce, set out a good deal of matter upon which at the present time judgment is suspended, and views which are undoubtedly speculative. He disclaims all responsibility for the accuracy of quoted work at times, and where it has seemed desirable, he has endeavored to place before his readers a judicial summing up of most questions. There are seventeen chapters and an Index. The first deals with the classification of bacteria. This is based upon the nomenclature adopted by the Society of American Bacteriologists and extended by Bergey in his textbook published in second edition in

1926, which represents a serious effort to unify bacterial classification and to combine the points of view of the general and medical bacteriologists. In this classification the *International Rules of Botanical Nomenclature* have been adopted in so far as they can be made to apply to bacteriology. The second chapter considers the streptococcus problem as shown in scarlet fever, erysipelas, puerperal sepsis and acute rheumatism. Chapter three treats of bacterial variation, chapter four of the bacteriophage, and five of experimental epidemiology. The remaining chapters treat successively of Calmette and B C G, ultra-microscopic and filter-passing viruses, diseases associated with Rickettsia bodies, measles and tularemia, recent work upon the pneumococci, spirochetal infections, local immunity and the work of Besredka, diphtheria and the anaerobic organisms. The most important work bearing upon the various subjects treated is well analyzed and digested, the discussion is fair and dispassionate, and the conclusions conservative and well-guarded. There seem to be some important omissions, for instance, the important work of Mellon on transmutation is not mentioned in the chapter on bacterial variation. The work of the last four years is not as thoroughly sifted as that of the war period and immediately following. This is a thoroughly useful little resumé of the recent advances in bacteriology, and very convenient for the general reader and for the student and teacher. The author's style is especially well adapted to a critical review of this kind, being clear and concise, and this added to his unprejudiced treatment, makes of it a very useful book.

*A Handbook of Clinical Pathology* By FRANK SCOTT FOWWEATHER, M D, M Sc, D P H (Liverpool), F I C, Lecturer in

Chemical Pathology, University of Leeds, Chemical Pathologist, Leeds General Infirmary With Foreword by Sir BERKELEY, Bt, KCMG, CB, President of the Royal College of Surgeons of England 216 pages, 18 illustrations P Blakiston's Son & Co, Philadelphia, 1929 Price in cloth \$3.00

This little volume is based on a course of lectures on clinical chemical pathology given to senior students of the Leeds University Medical School. In presenting them in this form it is hoped that they will serve as a short textbook on the subject which may be of use not only to medical students but to house surgeons and house physicians and to general practitioners. The book is not a handbook for laboratory workers since no attempt is made to describe methods of chemical analysis, nor is it intended to be a guide for research workers. It is intended primarily for the clinician, who should have a clear knowledge of the help he may expect from laboratory tests, of their limitations and of the conditions to be observed in order to get the best results from them. In other words, the clinician should know when to have the tests made, how to obtain the necessary specimens and how to interpret the results. It is with the object of offering information on these points that the book has primarily been written. Actual chemical work may be left in the hands of the expert. The book represents a fairly complete resumé of modern clinical chemistry along the lines indicated above. The material embraced in it is fairly complete, although some important omissions are noted. Taken all in all it fulfills the functions for which it was written very adequately, and may be recommended for this purpose. Its chief advantage is its simplicity of treatment.

*Morphologic Variation and the Rate of Growth of Bacteria* Volume I of Microbiology Monographs General Agricultural Industrial By ARTHUR T. HENRICI, M.D., Professor of Bacteriology, University of Minnesota 208 pages, 36 illustrations,

27 tables, 89 references Charles C. Thomas, Springfield-Baltimore, 1928 Price in cloth \$3.00 net

This is the first volume of a series of Monographs on General, Agricultural and Industrial Microbiology, edited by R. E. Buchanan of Iowa State College, E. B. Fred of Wisconsin and S. A. Waksman of Rutgers. These monographs will aim to present the subject of microbiology in the form of a series of monographs by authors of repute and authority in an authoritative and serviceable manner. These will treat of certain phases of microbiology in general or of personal investigations that can be treated in a monographic manner. The first volume is concerned with morphologic variation and the rate of growth of bacteria, one of the most important problems of the bacteriology of today. It is a record of personal researches undertaken with the hope that by the "magic of numbers" some order might be brought out of the chaos which has so far filled that field of bacteriology which has to deal with the form and structure of bacterial cells. The dogma of monomorphism has dominated the field of bacteriologic thought since the acceptance of the Cohn-Koch doctrine of the constancy of cell forms and the immutability of bacterial species, which has discouraged all investigation of problems of morphology, inheritance and variation in bacteria for a good many years. It is to be looked upon as a healthy sign that within recent years, through the activities of a small but persistent group of modern pleomorphists, bacteriology is at last definitely breaking away from the old tradition, and is seriously reopening for discussion and investigation the old problem of morphologic variation in bacteria. This movement has within it that danger inherent in all revolutionary movements, the tendency to go too far in the opposite direction. In the writings of at least some of the new pleomorphists, their protests to the contrary notwithstanding, there is clearly evident a tendency to return to the pre-Koch idea that any bacterium may transmute to the form of any other. It is high time, there-

## Reviews

fore, that we stop to evaluate the data and critically analyze the logic of the disciples of the "newer biology" of bacteria. The work of the latter investigators have probably not convinced more than a few that bacteria exhibit complex fungoid life cycles, but they demonstrated beyond all question that bacteria do regularly show pronounced morphologic variations, the nature and significance of which must be determined before we can make any real progress towards understanding the fundamental biologic problems of the group. In this work Henrici shows that bacterial cells are constantly changing in size and form and structure, but instead of these changes occurring in a haphazard or meaningless fashion, or instead of being phases of a rather vague and complex life cycle, they occur with great regularity, and are governed by relatively simple laws which, after more data have been accumulated and analyzed, may probably be very precisely formulated. Henrici's investigations indicate that the growth of bacteria in artificial cultures is governed by the same laws as govern the development of a multicellular organism, that their cells during growth pass through exactly the same sort of a developmental cycle as the cells of a plant or animal, exhibiting in turn an embryonic form during the period of slow growth or rest, and a senescent form during the period of "cytomorphosis" in populations of free unicellular organisms differing only in degree from that of multicellular individuals. If this hypothesis be accepted it must prove of great importance in general biology, for it carries with it the implication that multicellular organisms are after all but populations of cells, whose organized individuality is a result, not a cause, of the differentiation of those cells. The morphologic variations of bacteria are therefore an expression of the variations in growth rate. The growth of a population of bacteria in a culture is apparently governed by the same laws that govern the growth of a multicellular individual; there is a close parallelism between the nature of the cell changes exhibited by a growing culture of bacteria and those which occur in a multicellular individual. If Henrici's views are correct, the monomorphistic theory without modification can no longer be held to be sound, but the theory of complex life cycles maintained by the pleomorphists remains to be proved by those who declare such life cycles to exist. The theory of cytomorphosis is not necessarily opposed to that of complex life cycles, rather the two viewpoints are rather different ways of looking at the same thing than that they are mutually exclusive. The ten chapters are concerned with: Problem of morphologic variation of bacteria, rate of growth of bacteria, technique, size of the cells of *Bac megatherium*, size and form of the cells of the colon bacillus, observations on a diphtheroid bacillus, note on spore formation, morphologic variations of the cholera vibrio, senescent forms of the colon bacillus, and cytomorphosis in bacteria. Henrici's monograph is a timely and valuable contribution to the vexed problem of bacterial variation. His work and logic seem very reasonable. It remains now for the pleomorphists to prove that his "age-forms" do actually represent stages in a complex sexual cycle.

*Thrombo-Angitis Obliterans Clinical, Physiologic and Pathologic Studies* By GEORGE E. BROWN and EDGAR V. ALLEN, Division of Medicine, Mayo Clinic, Collaborating in Pathology with HOWARD R. MAHORNER, Fellow in Surgery, The Mayo Foundation. 219 pages, 61 figures, 12 tables, and 1 colored plate. W. B. Saunders Company, Philadelphia, 1923. Price in cloth \$3.00.

This study is based on observations made on more than 300 cases of thrombo-angitis obliterans seen in the Mayo Clinic in the years 1922 to 1927 inclusive. Each year has seen an increase in the number of cases recorded in this clinic, at present the ratio of patients with this disease to all males registering is approximately 1:400. The study includes the pathologic examination of fifty amputated specimens, twenty-seven

of which were studied by Mahorner. The comparatively recent recognition of the disease, its peculiar sex and age frequency, together with the racial predilection and the probability of its increasing incidence have led to a greatly increased interest in this disease. There are thirteen chapters in the book, treating of the history of the disease, its etiology and pathology, clinical course and clinical types, analysis of symptoms, erroneous interpretations of symptoms, history taking and examination, diagnosis, miscellaneous studies, treatment, prognosis and special methods of investigation. These chapters are followed by a bibliography and index. In the first few years of the authors' experience practically all of the cases observed were associated with severe degrees of gangrene. Owing to a wider appreciation of the existence of thrombo-angitis by the medical profession a larger number of cases are now seen in the stages before the appearance of trophic disturbances and gangrene. The institution of prophylactic and physical measures in the early stages of the disease, the realization of the importance of rest, the use of nonspecific protein therapy, and the application of surgical measures to the sympathetic nervous system in selected cases, have prevented many amputations and have afforded a more optimistic prognosis. The etiologic agent in thrombo-angitis obliterans is still unknown, and more work remains to be done on the problems of anoxemia in relation to claudication and thrombosis. This volume is a valuable contribution to the subject of vascular diseases, and it cannot fail to be interesting and valuable to both internist and surgeon. The various chapters are thoroughly up to date and constitute a very complete description of the disease. Of interest is the well-known association of tobacco smoking, and the probabilities of the increase of the disease due to the present wide-spread abuse of this habit. The book is clearly and concisely written, the illustrations are to the point and are most useful. The authors believe that the disease primarily falls into the realm of the internist, but that the

close association of surgeons and internists is important.

*Nephritis*. By HERMAN ELWYN, M.D., Assistant Visiting Physician, Gouverneur Hospital, New York. 347 pages, 2 figures. The MacMillan Company, New York, 1929. Price in cloth \$4.00.

This is a reprinting of this work on nephritis which was first published in 1926. In it Elwyn presents the individual forms of nephritis with an attempt at correlation of the clinical phenomena with the pathologic changes. As a necessary preliminary to such a presentation he discusses the normal function of the kidney, renal insufficiency, hypertension and uremia, which make up the first four chapters. Chapter five is concerned with the classification of nephritis, chapter six with embolic glomerulonephritis, chapter seven with non-embolic glomerulonephritis, chapter eight with acute diffuse glomerulonephritis, chapter nine treats of the subacute and subchronic forms of diffuse glomerulonephritis, and chapter ten with chronic diffuse glomerulonephritis. The remaining chapters discuss the kidney of pregnancy, lipoid nephrosis, amyloid nephrosis, the bichloride kidney, the pathology, etiology and pathogenesis of arteriosclerosis, renal arteriosclerosis with and without renal insufficiency and the syndrome of benign hypertension. In discussing the kidney of pregnancy the author ventures to offer a new explanation for the occurrence of eclampsia in pregnancy. Elwyn follows Volhard very closely in the correlation of the fundamental pathologic and chemical changes in the various forms of nephritis with the clinical phenomena. During the last twenty-five years our knowledge of nephritis has been much advanced, in this book this advance of knowledge on this important subject is brought together and very clearly presented. It is a thoroughly practical and valuable presentation of the subject from the modern standpoint.

*Spinal Anesthesia* (Subarachnoid Radicular Conduction Block), *Principles and Technique*. By CHARLES H. EVANS, M.D.,

## Reviews

Clinical Assistant, N Y Postgraduate Medical School and Hospital, Lying-in Hospital of the City of New York, Assistant Surgeon, N J Orthopedic Hospital, Orange Introduction by W WAYNE BABCOCK, MD, FACS Foreword by CHARLES GORDON HEYD, MD, FACS 203 pages, 41 illustration, 3 in color, one folding colored plate Paul B Hoeber, Inc, New York, 1929 Price in cloth \$5 50 net

In this volume the author attempts a survey of the literature which has appeared upon this subject, and combines with it the results of his own personal experience in spinal anesthesia. In spite of the large amount of research and the numerous articles upon spinal anesthesia that have appeared during the last twenty-five years, there has been very little effort made to put the present knowledge of the subject into concise form available to the medical profession. There are excellent summaries on spinal anesthesia which are lost to the profession because the literature containing the material is found scattered throughout the specialties of medicine. The original purpose of the author was to collect data for a short manuscript to be used as a guide at the N Y Postgraduate Hospital. The patients undergoing surgical operations under this form of anesthesia were carefully studied, especially as to the psychologic changes taking place both at the time of operation and afterwards, the immediate physiochemical relations and the postoperative convalescence. Further study led to this monograph, which the author hopes will be the means of aiding other surgeons who may desire to employ spinal anesthesia in their practice. The author is convinced that not only is spinal anesthesia safe, but that it is the most satisfactory of all forms of anesthesia for certain surgical procedures. He has selected efficient technical methods from the many advocated, and this book will be found of great value by those who would prepare themselves for the use of spinal anesthesia. Its perusal will give all necessary information as to when, how,

and why the surgeon should employ spinal anesthesia

*Thyroxine* By EDWARD C KENDALL, M S, Ph D, D Sc, The Mayo Foundation, Rochester, Minnesota American Chemical Society Monographs 225 pages The Chemical Catalog Company, Inc, New York, 1929 Price in cloth \$5 50

This volume is an American Chemical Society Monograph which was advertised in 1919, but because of the prolongation of the chemical investigation of thyroxine appears now as the forty-seventh of the published series of monographs. Much of the work which is presented, however, has been completed in the last two or three years, and any monograph on the chemistry of the thyroid prepared before the present year would have been out of date almost before the printing had been completed. What has been assembled in the monograph has been chosen from the viewpoint of the chemist and with a desire to correlate the activity of the thyroid gland with reactions which involve oxidation. The story of thyroxine is told in this monograph up to the time of its production in a pure form by the English observers, Harington and Barger, in 1927, who showed that thyroxine is a tetra-iodo derivative of oxyphenyl tyrosine, and were able to produce it synthetically. These observers also showed that the physiological activity of the synthetic product is identical with that of the natural product. Thyroxine has a definite place in the study of normal and abnormal mental processes. Whether or not it functions as an enzyme or influences the velocity of enzyme may be a matter for controversy, but the processes which it does affect can be shown to be of fundamental importance, not only to the physiologic activities of man, the social and economic activities of man. The theoretical deductions in this monograph have been largely based on the goiter work of the Mayo Clinic. The author himself regards it "as the photograph of an ever-changing scene." There are many questions left unanswered, time will bring many additions and possibly many alterations.

# College News Notes

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## PROGRAM THIRTEENTH ANNUAL CLINICAL SESSION

### BOSTON COMMITTEES

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#### PRELIMINARY PROGRAM

#### ANNUAL CLINICAL SESSION

#### THE AMERICAN COLLEGE OF PHYSICIANS

APRIL 8-12, 1929

Monday, April 8, 1929

OPENING SESSION, 2 30 O'CLOCK

Hotel Statler Ballroom

1 Addresses of Welcome David L Edsall, Dean of Harvard Medical School  
Alexander S Begg, Dean of Boston University Medical School  
A Warren Stearns, Dean of Tufts College Medical School

John M Birnie, President of Massachusetts Medical Society  
Lincoln Davis, President of Suffolk District Medical Society

2 Reply to Addresses of Welcome  
Charles F Martin, President of The American College of Physicians

3 Tuberculosis A Confession of Faith.  
Lawrason Brown, Saranac Lake, N. Y.

4 (Title not yet announced) Lewellys F Barker, Baltimore

5 Juvenile Diabetes I M Rabinowitch, Montreal

6 Glycosuria James E Paullin, Atlanta

7 Clinical Aspects of Paroxysmal Hypertension M C Pincoffs, Baltimore

EVENING SESSION, 8 00 O'CLOCK  
Hotel Statler Ballroom

*Symposium on Deficiency Diseases*

1 The Fundamental Nature of Deficiencies George R Minot, Boston

2 Pathology of Deficiencies. S Burt Wolbach, Boston

3 Biochemistry and Physiology of Deficiencies George R. Cowgill, New Haven

4 Pernicious Anemia Randolph West, New York

Tuesday, April 9, 1929  
MORNING, 9 00 TO 12 00 O'CLOCK  
Hospital Clinics

AFTERNOON, 2 30 TO 5 00 O'CLOCK  
Hotel Statler Ballroom

1 Fatigue and Infection W L Holman, Toronto

2. Neoplasms J B Murphy, New York

3 Specific Dynamic Action of Protein, Fat and Carbohydrate in Altered States of Nutrition. Edward H Mason, Montreal

4 The Relation of Neisserian Infection to the Various Types of Arthritis O H Perry Pepper, Philadelphia

5 The Fallacy of Vaccine Therapy Charles C Bass, New Orleans

6 The Treatment of Angina Pectoris Harlow Brooks, New York

7 The Coronary Problem. Arthur R Elliott, Chicago

8. Clinical Aspects of Trachiniasis. Lewis A. Connor, New York.

9 An Intensive Clinical Study of a Graphic Method of Recording Blood Pressure. Louis F Bishop and Louis F. Bishop, Jr., New York

EVENING SESSION, 8 00 O'CLOCK  
Hotel Statler Ballroom

1 Psychiatry in Relation to Medicine. Austin F Riggs, Stockbridge, Mass

2 Syphilis of the Adrenals and Its Relationship to the So-called Idiopathic Addison's Disease. Aldred S Warthin, Ann Arbor.

3. Lung Syphilis R I Rizer, Minneapolis.

A smoker will follow this session.

Wednesday, April 10, 1929  
MORNING, 9 00 TO 12 00 O'CLOCK  
Hospital Clinics

AFTERNOON, 2 30 O'CLOCK  
Hotel Statler Ballroom

1 The Treatment of General Paresis Harry C Solomon, Boston.

2 Psychiatry's Part in Preventive Medicine. Arthur H Ruggles, Providence

3 The Need of Emotional Data in the Medical History John Favill, Chicago.

4 Milder Forms of Coronary Obstruction James B Herrick, Chicago.

5 The Failing Heart of Middle Life David Riesman, Philadelphia.

6 Hypertension George C. Hale, London, Ont

7 Undulant Fever in the United States George Blumer, New Haven.

8. (Title not yet announced) Robert A Cooke, New York

9 Tobacco Smoking and Gastric Symptoms Irving Gray, Brooklyn

EVENING SESSION, 8 00 O'CLOCK  
Hotel Statler Ballroom

1. Serums and Vaccines in the Prevention and Treatment of Disease. Benjamin White, Boston

2 Clinico-Roentgenological Conference M C Sosman and Associates, Boston.

Thursday, April 11, 1929  
MORNING, 9 00 TO 12 00 O'CLOCK  
Hospital Clinics

AFTERNOON, 2 30 O'CLOCK  
Hotel Statler Ballroom

1 The Treatment of Acute Asphyxia. Cecil K. Drinker, Boston

2 The Significance of Abnormal Metabolic Features in the Management of Thyrotoxicosis Walter W Palmer, New York

3 Can or Will the Internist Practice Preventive Medicine? George H Bigelow, Boston

4 Factors in the Prognosis of High Blood Pressure W W Herrick, New York

5 The Carotid Sinus Reflex (Hering), Its Use in the Diagnosis and Treatment of Certain Cardiovascular Diseases C Saul Danzer, Brooklyn

6 Lead Poisoning from Snuff Raymond J Reitzel, Galveston

The General Business Meeting of The College will be held at 4 00 in the Hotel Statler Ballroom All Masters and Fellows should attend

#### EVENING, 7 00 O'CLOCK

Annual Banquet of The College

To be followed by a Dance

Address George E Vincent, President of Rockefeller Foundation

Friday, April 12, 1929

MORNING, 9 00 TO 12 00 O'CLOCK

Hospital Clinics

AFTERNOON, 2 30 O'CLOCK

Hotel Statler Ballroom

1 Motion Picture Demonstrating Its Value in Teaching Electrocardiographic Interpretations of Cardiac Arrhythmias Joseph B Wolfe, Philadelphia

2 Dr William Dunlop and Pioneer Canadian Medicine J W Crane, London, Ont

3 Rheumatic Fever Homer F Swift, New York

4 (Title not yet announced) J. C Meakins, Montreal

5 Results to Be Expected in Malignant Disease Treated by Radiotherapy George E Pfahler, Philadelphia

6 The Problem of the Nervous Patient Charles H Nielson, St. Louis

7 Endogenous Obesity—A Misconception L H Newburgh and M W Johnston, Ann Arbor

#### EVENING SESSION, 8 00 O'CLOCK

Hotel Statler Ballroom

Convocation Exercises

The General Profession is cordially invited No special admission tickets are required

1 Convocation Ceremony

2 President's Address Charles F Martin, Montreal

### PRELIMINARY PROGRAM OF SPECIAL CLINICS AND DEMONSTRATIONS

This year the general session will be held in the afternoons and evenings, while clinics and demonstrations will be held in the mornings from 9 00 to 12 00

Special Admission Cards required Clinic reservation forms and full directions will accompany the Final Program Reservations may be made by mail or daily at the Registration Bureau

Special clinics and demonstrations will be held as follows

A

#### BETH ISRAEL HOSPITAL

Program in charge of Herrman L Blumgart



## B

## BOSTON CITY HOSPITAL

1. (A guest will give a clinic at this time; the name will be announced later.)

2. The Progress of the Boston City Hospital John J. Dowling, Superintendent

3. Treatment of Pneumonia. Demonstration of Cases Edwin A. Locke

4. Clinic of Unusual Cases Francis W. Palfrey.

5. Pernicious Anemia Demonstration of Cases. William B. Castle.

6. Treatment of Anemias Demonstration of Cases George R. Minot.

WEDNESDAY, APRIL 10, 1929

1. (A guest will give a clinic at this time; the name will be announced later.)

2. Gastro-Intestinal Cases. Franklin W. White.

3. Cardiac Cases William H. Robey.

4. Nephritis Cases. William R. Ohler

5. The Surgical Treatment of Pulmonary Tuberculosis. Demonstration of Cases Edward D. Churchill

Hypertension and Arteriosclerosis Demonstration of Cases Soma Weiss.

THURSDAY, APRIL 11, 1929

1. Cardiac Cases. Edward N. Libby and Thomas J. O'Brien.

2. A Case Illustrating the Value of the Electrocardiogram James M. Faulkner

3. Epilepsy William G. Lennox

4. Diseases of the Coronary Vessels. Demonstration of Cases Joseph T. Wearn.

5. Peptic Ulcer Demonstration of Cases. Maurice Fremont-Smith.

6. Neurological Cases Stanley Cobb

7. (A guest will give a clinic at this time; the name will be announced later.)

FRIDAY, APRIL 12, 1929

1. (A guest will give a clinic at this time; the name will be announced later.)

2. Cases of Disease of the Hemopoietic System Ralph C. Larrabee.

3. Lymphoblastoma Demonstration of Cases Henry Jackson, Jr.

4. Tropical Diseases Demonstration of Cases George C. Shattuck.

5. Fluoroscopic Diagnosis in Chest Conditions Demonstration of Cases Harold W. Dana

6. Carcinoma of the Head of the Pancreas Demonstration of Cases Irving J. Walker

## C

BOSTON CITY HOSPITAL  
THORNDIKE MEMORIAL LABORATORY

WEDNESDAY AND THURSDAY

APRIL 10 AND 11

BETWEEN 10 30 AND 12 30

Demonstration of Researches Concerning the Following Topics

Dr. Castle and Associates	Anemia
Dr. Jackson and Associates.	Malignant Tumors
Dr. Lawrence and Associates	The Physiology and Pathology of White Cells
Dr. Lennox	Epilepsy
Dr. Minot and Associates	The Blood
Dr. Nye and Associates	Bacteriological Problems
Dr. Wearn and Associates.	The Capillaries
Dr. Weiss and Associates	Vascular Problems

BOSTON CITY HOSPITAL  
SOUTH DEPARTMENT

Program in charge of Edwin H Place

Ward visits on (1) diphtheria, (2) scarlet fever, (3) a few of the other minor groups such as chicken pox, mumps, measles and whooping cough

Amphitheater demonstration of cases of chronic laryngeal injury and other damages resulting from contagious diseases

E

BOSTON DISPENSARY

TUESDAY, APRIL 9, 1929

- |  |  |
|--|--|
| 1 Heart Disease David Davis            | 4 Chronic Pancreatic Disease Bert B Hershenson |
| 2 Essential Hypertonia David Ayman     | 5 Tuberculosis H Louis Kramer                  |
| 3 Neurological Clinic A Warren Stearns |  |

- 4 Obesity Mark Falcon-Lesses  
5 Gastro-Intestinal Clinic Percy B Davidson

THURSDAY, APRIL 11, 1929

- 1 Neurosyphilis Arthur Beck  
2 Neurasthenia Joseph H Kaplan  
3 Nephrosis Tobert W Buck  
4 Domiciliary Medicine in Clinical Teaching—Selected Case Osadore Olef  
5 Domiciliary Medicine in Clinical Teaching—Selected Case Charles Korb  
6 Diabetes James H Townsend

WEDNESDAY, APRIL 10, 1929

- 1 Bronchiectasis William Dameshek  
2 Psychalgia Joseph H Pratt  
3 Arthritis John D Adams

F

CHILDREN'S HOSPITAL

Program in charge of Kenneth D Blackfan

G

HOMEOPATHIC HOSPITAL  
EVANS MEMORIAL CLINIC

TUESDAY, APRIL 9, 1929

- 1 Sterility Clinic Special Emphasis to be Placed on the Constitutional Factors in Sterility S R Meaker and A W Rowe

WEDNESDAY, APRIL 10, 1929

*Endocrine Clinic*

- 1 Endocrine Diagnosis and Therapy Charles H Lawrence  
2 Endocrine Disorders Associated with Otosclerosis and the Menière Syndrome D W Drury  
3 Eye Findings in Endocrine Disorders W D Rowland  
4 Cases Presenting Outward Evidence of Endocrine Disorders Found on Study not to have Endocrine Disturbance A W Rowe

- 5 Dementia Praecox L G Hoskins  
6 The Follicular Hormone J C Janney  
7 Discussion on Sugar Metabolism as Influenced by Insulin in Pituitary Disease H Ulrich and A W Rowe

THURSDAY, APRIL 11, 1929

*General Medical Clinic*

- 1 Heart Clinic W D Reid  
2 Intestinal Migraine C W McClure  
3 Neurology N H Garrick  
4 Lung Abscess, Diagnosis and Treatment Bronchoscopy, the Use of the Bronchoscope in Diagnosis and Treatment. L R Johnson

FRIDAY, APRIL 12, 1929

(Program to be announced later)

## College News Notes

H

- 1 Clinic by James E. Paullin, Atlanta
- 2 Thoracic Clinic Frederick T. Lord
- 3 Cases of Hypertension William B. Breed
- 4 Cardiac Clinic Howard B. Sprague
- 5 Endocrine Clinic Walter Bauer and Dwight L. Sisco

WEDNESDAY, APRIL 10, 1929

- 1 Clinic by Lewellys F. Barker, Baltimore
- 2 Demonstration of Medical Cases William B. Robbins.
- 3 Pediatric Clinic Fritz B. Talbot and Harold L. Higgins
- 4 Clinico-pathological conference Richard C. Cabot and Tracy B. Mallory
- 5 Diabetic Clinic Roy R. Wheeler

I

NEW ENGLAND BAPTIST HOSPITAL  
Program in charge of Albert A. Hornor

J

NEW ENGLAND DEACONESS HOSPITAL  
Program in charge of Elliott P. Joslin

- 1 Carcinoma of the Colon and Colitis from the Surgical Point of View Daniel F. Jones
- 2 Gastro-Intestinal Cases Sara M. Jordan and Chester Kiefer.
- 3 Thyroid Cases Frank H. Lahey
- 4 Pedigreed Diabetics Elliott P. Joslin.
- 5 Surgery in Diabetics L. S. McKittick
- 6 The Pathology of Diabetes Shields Warren

There will be further additions to this program including clinics by larynologists, ophthalmologists, gynecologists and roentgenologists

K

## PETER BENT BRIGHAM HOSPITAL

1. Diagnosis of Certain Forms of Heart Disease. Lewis A. Corner, New York
- 2 Chronic Myocardial Disease Henry A. Christian.
- 3 Results of Treatment of Duodenal Ulcer H. S. Emery.
- 4 Some Considerations on the Relation of Cardio-Renal System to Surgery of the Urinary Organs William S. Quimby
5. Bronchoscopy in Lung Disease Herman C. Richards

## MASSACHUSETTS GENERAL HOSPITAL

THURSDAY, APRIL 11, 1929

- 1 Clinic by O. H. Perry Pepper, Philadelphia
- 2 Neurological Clinic James B. Ayer
- 3 Psychotherapy of Gastro-Intestinal Diseases William Herman
- 4 Gastro-Intestinal Clinic Chester M. Jones
- 5 Indications for Splenectomy Arlie V. Bock
- 6 Cases of Pernicious Anemia Wyman Richardson

FRIDAY, APRIL 12, 1929

- 1 Clinic by J. C. Meakins, Montreal.
- 2 Demonstration of Cases Gerald Blake
- 3 Medical Clinic James H. Means
- 4 Demonstration of Cases F. Dennette
- 5 Anaphylaxis Clinic Francis M. Rackemann

## WEDNESDAY, APRIL 10, 1929

- 1 Cardiac Disease, the Result of Infectious Processes James B Herrick, Chicago
- 2 Gallbladder Disease Channing Frothingham
- 3 Bronchial Asthma I Chandler Walker.
- 4 Anemia William P Murphy
- 5 Thrombophlebitis John Homans

## THURSDAY, APRIL 11, 1929

- 1 Mitral Stenosis David Riesman, Philadelphia
- 2 Signs of Persisting Infection in Acute Rheumatic Fever Clifford L Derick

- 3 Hemorrhagic Nephritis James P O'Hare
- 4 A Surgeon's Views of the Treatment of Peptic Ulcer David Cheever
- 5 Neurosurgical Conditions Harvey Cushing

## FRIDAY, APRIL 12, 1929

- 1 Hypertension Charles F Martin, Montreal
- 2 Vascular Disease in Diabetes Mellitus Reginald Fitz
- 3 Treatment of Certain Types of Cardiac Arrhythmia Samuel A Levine
- 4 Treatment of Trifacial Neuralgia. Gilbert Horrax
- 5 Diuretics Henry A Christian

L

## ROBERT BRECK BRIGHAM HOSPITAL

Program in charge of Louis M Spears  
Clinics on Arthritis

M

## UNITED STATES NAVAL HOSPITAL

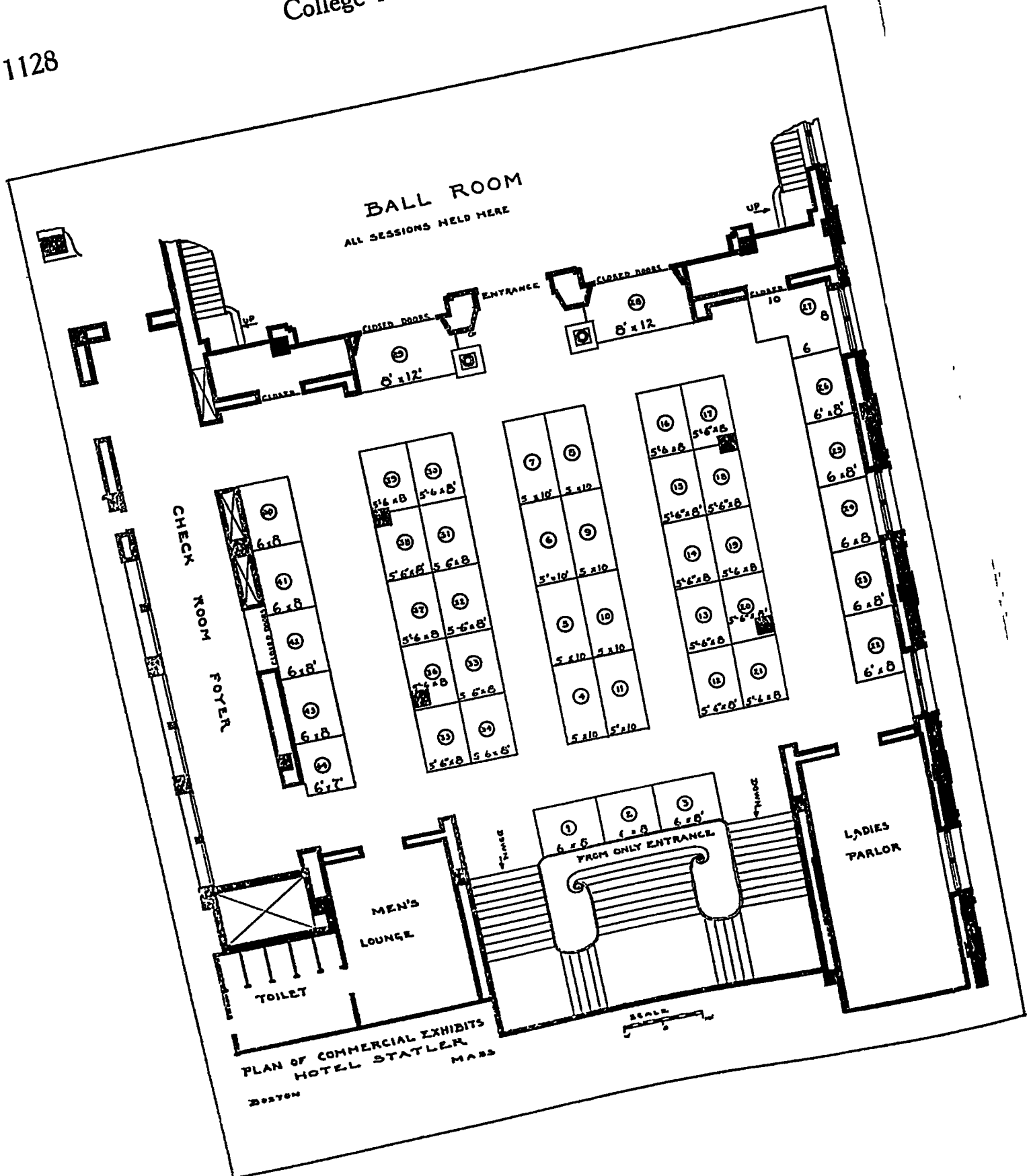
Program in charge of Capt F L Pleadwell, MC, U S N

Presentation of medical cases in the conference room of the hospital each morning. Following this the group will be split up in sections of five Each section will be in charge of a ward medical officer, and the balance of the morning will be devoted to ward rounds

## TECHNICAL EXHIBIT

The technical exhibits have been arranged by the Executive Secretary, Mr E R Loveland, and the following chart shows the arrangement of booths and the assignment to exhibitors from various parts of the country The exhibits are highly diversified in their variety and will bring to the attendants at the Clinical Session, the latest and most improved equipment, the best pharmaceutical products, almost the whole library of medical publications and many other products of special interest to the Internist, Pediatrician, Neurologist, Psychiatrist, Radiologist and research worker

This Exhibit is undoubtedly the best arranged and the most popular one that The College has yet had The location is in the Ballroom Foyer where all attendants to the meeting will pass through the exhibits daily The Joseph T Griffin Decorating Company, of Louisville, Kentucky, who installed the exhibits for the American Medical Association, the Southern Medical Association and many other prominent medical societies, will be in charge of the booths and decorations



## LIST OF EXHIBITORS

SPACE	NAME	CITY AND STATE	PRODUCT
20	Abbott Laboratories	North Chicago, Ill	Pharmaceutical Products
12 & 21	D Appleton & Company	New York, N Y	Medical Publications
31	The Battle Creek Food Company	Battle Creek, Mich	Health Foods
22	Bausch & Lomb Optical Co	Rochester, N Y.	Microscopes, Photomicro & Projection Apparatus
40	P Blakiston's Son & Co	Philadelphia, Pa	Medical Publications
13	The Borden Sales Company, Inc	New York, N Y	Merrill Soule Infant Foods
26	Britesun, Inc	Chicago, Ill	Therapeutic Lamps
25	Cambridge Instrument Co., Inc	New York, N Y	Electrocardiographs & Accessories, and other Physiological Instruments
3	Cameron's Surgical Specialty Co	Chicago, Ill	Electro-Diagnostic Surgical & Dental Instruments
44	G W Carrick Co	Newark, N J	Pharmaceutical Products
1	Warren E Collins, Inc	Boston, Mass	Metabolism and Oxygen
49	Davies, Rose & Co., Ltd	Boston, Mass	Trethylene, Pil Digitalis, Shadocal
14	F A Davis Company	Philadelphia, Pa	Medical Publications
16	Deshell Laboratories, Inc	Chicago, Ill	"Petrolagar"
42 & 43	General X-Ray Company	Boston, Mass	"Morse" Wave Generator, GX-Galvane-Faradise Plate, Diathermy Apparatus, Electrodes
34	Paul B Hoeber, Inc	New York, N Y	Medical Publications
19	Horlick's Malted Milk Corporation	Racine, Wis	Malted Milk Products
17	Kalak Water Company, Inc	New York, N Y	Kalak Water
4	Charles B Knox Gelatine Co., Inc	Johnstown, N Y	Knox Gelatine
15	Lavoris Chemical Company	Minneapolis, Minn	"Lavoris"
45	LaMotte Chemical Products Co	Baltimore, Md	LaMotte Blood Chemistry Outfits
30	Lea & Febiger	Philadelphia, Pa	Medical Publications
47	Lederle Antitoxin Laboratories	New York, N Y	Biological Products and Pharmaceutical Specialties
9	J B Lippincott Company	Philadelphia, Pa	Medical Publications

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## BAUSCH &amp; LOMB CO

Booth 22

In each issue of this publication for the past few months, this space has been devoted to a brief description of a partial list of the optical instruments which Bausch & Lomb manufacture for the medical Profession

At the American College of Physicians meeting, April 8-12, 1929, the instruments which have been described herein will be on exhibit. A list of the instruments to be exhibited are

Microscopes  
Microtomes  
Colorimeters

Hemoglobinometers  
Centrifuges  
Haemacytometers

The physician who is contemplating buying new instruments will find this exhibition an excellent place to make his choice. Undoubtedly some who do not intend to purchase will be able to obtain a great deal of useful information on new instruments and improved methods, which should aid them in their practice.

Literature which will give a comprehensive knowledge of the latest developments in the field can be had at the Bausch & Lomb booth. If, however, you do not attend the meeting, the literature will be sent to you upon application to the Company.

## P BLAKISTON'S SON &amp; CO

Booth 40

The translation of Kaufmann's Pathology by Dr Stanley P Reimann, published by Blakiston in January, makes available to all American physicians and scientists a work of international repute, whose usefulness has been confined previously to those having a high aptitude for scientific German. The work is a most complete human pathology, general and special. Subjects of most importance to the practicing physician are emphasized and given in great detail. The work is in three volumes and contains 1072 illustrations, those of the last German edition being amplified by many unique pictures drawn by the staff artist at the Lankenau Hospital. A descriptive prospectus will be sent by the publisher upon request.

## THE BORDEN SALES COMPANY, Inc

Booth 13

In 1856 the first successful process for condensing milk was patented by Gail Borden. Today, 73 years later, the annual world production of all forms of concentrated milk amounts to more than three billion pounds, of which approximately 60 per cent is manufactured in the United States. The Borden Company continues to be the leading producer and distributor of condensed, evaporated, powdered and malted milks, and other milk products.

## DESHELL LABORATORIES, Inc

Booth 16

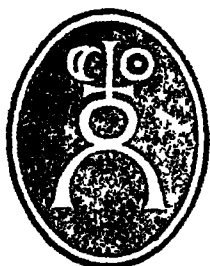
Prominent among the exhibits at the next Clinical Session will be Petrolagar—the emulsion of mineral oil.

Samples and literature pertaining to the wide application and usefulness of Petrolagar may be obtained by addressing 536 Lake Shore Drive, Chicago, Illinois.



## THE WM S. MERRELL COMPANY

Booth 23



This is the new symbol of the Wm S Merrell Company as they have begun their second century in the preparation of medicines for the use of the medical profession. This symbol is the sign used by the ancient alchemists to represent that by which perfection may be attained, the accomplishment of the ideal, the reward to those who faithfully follow the laws of their Philosophy.

The Merrell Symbol was also used by the Alchemists to represent the Elixir of Life, which, if taken according to instructions, would heal the sick and renew the life of the old. Needless to say, such an Elixir remained as an ideal and was never found. The development of rational Therapeutic agents in the closest approximation of the ideal that has as yet been made.

## SANBORN COMPANY

— 27 —

METABOLISM testing with simplified apparatus giving reliable data for diagnosis will be demonstrated at Space 27 by Sanborn Company. This Company manufactures and supplies directly to physicians and hospitals. Medical conventions afford special opportunity for Sanborn owners and prospective owners to get practical information of the latest and best methods of testing. The new and approved Sanborn ELECTROCARDIOGRAPH—portable and transportable models—the least expensive but the best, will gladly be explained. Visit Space 27.

## TAYLOR INSTRUMENT COMPANY

— 51 —

One of the exhibits by the Taylor Instrument Companies will be the Tycos Sphygmomanometer.

The Tycos Recording Sphygmomanometer introduces a means of measuring blood pressure which necessitates neither stethoscope nor indicator, its automatic nature insuring an exactness of systolic and diastolic pressure points never before attained.

In addition, any cardiac irregularity producing characteristic changes in the brachial artery is identified by the Tycos tracing.

This is best realized by an inspection of the actual graphs of various pathologies, which are included in their latest booklet, "The Clinical Use of the Tycos Recording Sphygmomanometer." Copy will be sent upon request.

SUBSCRIPTION DINNER AND MEETING  
of theSOUTHERN CALIFORNIA MEMBERS  
of the

## AMERICAN COLLEGE OF PHYSICIANS

The Southern California Fellows and Associates of the American College of Physicians gathered together at dinner on Friday evening, January 18, at the California Club, Los Angeles. Among those present were Dr. Leonard Rowntree, Rochester, Minnesota; Dr. William Engelbach, formerly of St. Louis, Mo.; Doctors Samuel Alter, Samuel Ayres, Charles C. Browning, Ralph

L. Byrnes, John V. Barrow, William F. Costolow, Egerton Crispin, Roland Cummings, Leland S. Chapman, Harry W. Coffin, Robert Cunningham, Kenneth Davis, Ernest Fishbaugh, Kendal Frost, George G. Hunter, Harold P. Hare, Carl R. Howson, Samuel I. Ingham, Joseph M. King, Henry H. Lissner, Ross Moore, Thomas J. Orbinson, Francis M. Pottenger, George Pincus, Leon Shulman, John M. Shuman, Harold H. Smith, Frederick Speik, Carl Sweet, Roy L. Thomas, Raymond G. Taylor, Giuseppe Verrellum, Walter Weiss, Edward R. Ware and John C. Webster, Los

Angeles, Frederick B Clarke, Long Beach, Edward W Hayes, Monrovia, Walter P Bliss, Joseph D Condit, John S Hibben, Arthur T Newcomb, Robert E Ramsay, Stephen Smith, Willard J Stone and John M Wilson, Pasadena, Paul E Simonds, Riverside, George S Langdon, San Bernardino, Hilmar O Koefod, Santa Barbara, Lyle C Kinney, Chancel L Lounsberry and Robert Pollock, San Diego

Following dinner Dr Egerton Crispin of the Board of Governors spoke on "Purposes and Ideals of the College" Dr F M Pottenger of the Board of Regents spoke on "The Future Plans of the College" The medical address of the evening on "Recent Advances in our Knowledge of the Liver" was given by Dr Leonard Rowntree, Director of Medical Service, Mayo Clinic, and Professor of Medicine in the University of Minnesota

#### DR ROBERT BERNHARD BECOMES LIFE MEMBER

Announcement is made that Dr Robert Bernhard (Fellow), New Orleans, Louisiana, has become a Life Member of the American College of Physicians by subscribing to the Life Membership Endowment Fund

Dr Noxon Toomey (Life Fellow), St Louis, read a paper on "Pruritus and Dermatitis of Internal Origin" before the Lee County Medical Society, Fort Madison, Iowa, on December 20

Dr L B McBrayer (Fellow) is the newly elected President of the Southern Pines (N C) Chamber of Commerce

Dr William Fitch Cheney (Fellow), San Francisco, has been elected President of the Commonwealth Club of California for 1929 This is a large social service club with nearly 5000 members, and this is the first time in the twenty-five years of its existence that a physician has been elected its President

Surgeon General Merritte W Ireland (Fellow) of the U S Army, was the prin-

cipal speaker at a meeting of the Indianapolis Medical Society, January 19, when they had as their guest Private John R Gissinger, of Huntington, Indiana, who volunteered to be bitten by infected mosquitoes during the Yellow Fever experiments in Cuba following the Spanish American War

Surgeon General Hugh S Cumming (Fellow) of the U S Public Health Service spoke before the section on Public Health and Industrial Medicine of the Philadelphia College of Physicians on January 18

Dr Samuel Weiss (Fellow), New York, demonstrated the new so-called gastric camera before the American-Hungarian Medical Association at the New York Academy on Medicine on December 18 Dr Weiss also demonstrated the gastric camera before one hundred physicians of New York City on December 22, the demonstrations being made on an inmate at the Sing Sing Prison

Dr Noxon Toomey (Life Fellow), St Louis, was recently elected Twelfth Supreme Eminent Master of the Chi Zeta Chi Medical Fraternity at the Twenty-fifth Anniversary Convention held in St Louis at the end of December

Dr Thomas G Simonton (Associate), Pittsburgh, President of the Pennsylvania State Medical Society, Dr Orlando H Petty (Fellow), Philadelphia, Dr H R M Landis (Fellow), Philadelphia, and Dr Elmer H Funk (Fellow), Philadelphia, were speakers on the program at the annual meeting of the Pennsylvania Tuberculosis Society at Pottsville, January 15 and 16

Dr Kenneth M Lynch (Fellow), Charleston, addressed the annual meeting of the Marlboro County Medical Society at Bennettsville (S C), January 10, on "Carcinoma of the Cervix Uteri"

Dr Joseph C Doane (Fellow), Philadelphia, addressed the Pennsylvania Conference on Social Welfare at Harrisburg during its Twenty-fifth Annual Session, February 13-16

Dr Solomon Solis Cohen (Fellow), Philadelphia, was the recipient of a gold medal at a dinner by the Phi Lambda Kappa Medical Fraternity, December 30, 1928

Dr Warren H Newcomb (Associate) recently resigned as health officer of Morgan County, Illinois

Dr Walter M Simpson (Fellow), Dayton, Ohio, addressed the Michigan Public Health Association at Lansing, January 9-10, on "Tularemia"

Dr Arthur C Morgan (Fellow), Philadelphia, was recently appointed Chairman of the disabled soldiers and medical aid committee of the Philadelphia County Council of the American Legion

Surgeon General Merritte W Ireland (Fellow) directed the recently completed history of the Army Medical Department during the World War Colonel Frank W Weed was Editor-in-Chief

Dr Noxon Toomey (Life Fellow), St Louis, published in the November, 1928, number of the *British Journal of Dermatology and Syphilis* an introductory article on his treatment of psoriasis by means of colloidal gold preparations

Dr Orlando H Petty (Fellow), Philadelphia, was installed as President of the Philadelphia County Medical Society on January 9

Dr Lewellys Barker (Fellow), Baltimore, was elected a Vice President for 1929 of the Pan-American Medical Association at its annual conference in Havana

Dr Leonard G Rowntree (Fellow), Rochester, Minnesota, and Dr Ernest C Fishbaugh (Fellow), Los Angeles, addressed the Los Angeles County Medical Association January 17

Dr Lyell C Kinney (Fellow), San Diego, addressed the San Bernardino County Medical Society recently

Dr George G Richards (Fellow), Salt Lake City, addressed the San Diego County Medical Society recently on ulcer of the stomach

Dr Gerald B Webb (Fellow), Colorado Springs, Colorado, delivered a lecture at the University of Maryland at Baltimore on January 3

Among Fellows of the College who addressed the forty-fifth annual meeting of the Tri-States Medical Association (including Arkansas, Mississippi and Tennessee) at Memphis, February 6-8, were Dr John H Musser, New Orleans, Dr Ray M Balyeat, Oklahoma City, Dr Frank Smithies, Chicago, Dr Lawrason Brown, Saranac Lake, Dr Arthur C Christie, Washington, Dr Henry K Dunham, Cincinnati; and Dr Leonard G Rowntree, Rochester, Minnesota

The American Public Health Association will hold its Fifty-Eighth Annual Meeting in Minneapolis, Minnesota, September 30 to October 5, 1929

Dr C R Jones (Fellow), Pittsburgh, delivered an address on "The Romance of Medicine" (illustrated), January 10, as one of a series of lectures sponsored by the Academy of Science and Art of Pittsburgh. Dr Jones is Professor of Principles of Medicine at the University of Pittsburgh, and for many years has been Treasurer of the American College of Physicians

Dr E A Hines (Fellow), Seneca, S C, was elected President of the South Carolina Pediatric Society at its annual meeting in Columbia, January 15 Dr Hines is the Secretary Editor of the South Carolina Medical Association

## OBITUARY

Joseph Sailer, Fellow of the American College of Physicians, died at his home in Philadelphia as the last hours of 1928 were spending themselves. He had attended the New Orleans meeting of the College where he read a paper on "Conditions Contra-indicating the Use of Digitalis." Very few appreciated at the time what an effort it must have been to prepare for and make this presentation. Although it was a tedious journey for him, he returned home considerably refreshed and apparently much better for having experienced a week of Southern hospitality. He undertook, against advice, the trip to Minnesota last June where he presided over the sessions of the Section on Gastroenterology of the American Medical Association. This effort too must have distressed him more than his friends realized at the time. After his summer holiday, he resumed with difficulty his usual active life and continued to do so up until about two months before his death. Thus it was, as no doubt he wished it to be, that he continued his life busied almost to the end in loyal service to his profession and patients.

"Joe" Sailer as he was familiarly called by his friends and students was born in the City of Brotherly Love somewhat over 61 years ago of a father and grandfather who were prominent in the financial life of the city. It was hoped that he too would follow in the footsteps of his fathers. After graduating from the Biological Department of the University of Pennsylvania in 1886 and giving banking a trial of eight months, he de-

cided however to study medicine, receiving his Medical Degree from the same University in 1891. Subsequent to this he spent four years as a resident in the Presbyterian and Philadelphia Hospitals in Philadelphia and as a student in Paris, Zurich and Vienna. During his European stay he worked in the laboratories of Déjerine, V. Monokow and Neisser. He was impressed at the time with the French school and especially enjoyed Charcot's instructions. Previous to entering the Medical School of the University of Pennsylvania he had spent a year in Germany learning her language.

After returning from Europe in 1895 he began to practice medicine as an associate of Dr. John Musser and at the same time became an Associate in Clinical Medicine in the Pepper Clinical Laboratory. He was at one time Assistant Pathologist at the Philadelphia Hospital and at other times Pathologist to the Pennsylvania Training School for Feeble Minded Children, Saint Joseph's and Maternity Hospitals in Philadelphia. He also taught in the Pathological Department of the University when Dr. Simon Flexner served as Professorship in this institution. In the Department of Medicine of his Alma Mater he rose from the position of Instructorship to that of a Clinical Professorship. At various times he was a physician to the Charity, Howard, Philadelphia, Polyclinic, University and Presbyterian Hospitals.

He was interested in the entire field of Internal Medicine, but as his

friends know, he passed through three distinct periods in his medical life when his efforts were more or less concentrated on some special phase of the larger field. During the first of these periods he showed a neurological bent, during the second, gastro-enterology seemed to be uppermost in his mind, while the final years of his life were distinctly cardiovascular in their coloring. In this latter period he was especially concerned in the organization of the Philadelphia Association for the Study and Prevention of Heart Disease as well as the larger national body having the same objective in view. He was instrumental in bringing about the construction of a new home for convalescent cardiac children which opened its doors during his last illness. This event must have given him much satisfaction and the home serves as a splendid memorial to his interest in cardiac disease and more especially those who fall victims of this malady.

His bibliography in the main shows very clearly the three interests he had in internal medicine. In 1891 his essay on "Ouabain" won the Medical News Prize. When he returned from Europe he began to write articles chiefly concerned with neurological observations both of a clinical and pathological nature. "Alterations in the Spinal Cord in Azoturia," "A Contribution to the Pathology of the Choroid Plexus," "Degenerative Changes in Nerve Cells" and Meralgia Paresthetica are some the contributions made during this first period. In 1901 his writings began to show his especial interest in the Gastrointestinal tract and the literature received his varied

observations on gastric secretion, pancreatitis, carcinoma, achylia gastrica, linitis plastica, visceroptosis and other subjects. From 1915 to the end, his major writings concerned the cardiovascular system. Scattered, however, throughout his writings appear papers concerning the field which was finally nearest his heart. Among these are articles dealing with aortic regurgitation, relative pulmonary insufficiency, aneurisms, the arrhythmias and other titles concerned with this system.

During the world war he served with distinction and kept busily observing and giving to the medical profession the result of his studies. In this period appeared with others, a paper on pneumococcus carriers, one on mumps, one on cerebrospinal meningitis and another on the group consultant. His bibliography numbers at least 125 articles, among which are found a very interesting contribution "On the State of Medicine as Depicted by Pepys in the Reign of Charles II" and a thoroughly fine one on "Genghis Khan."

Besides his tremendous interest in medicine Dr. Sailer took much pleasure in the collection of books and line engravings. Of the latter he had accumulated a very noteworthy number of fine examples.

All who knew him were impressed by his fineness of character, by his gentility and by his tremendous fund of information which seemed to embrace every field of knowledge. With it all he was modest and never ostentatious. His undergraduate students loved him and respected him. This love and respect was held by his medical confreres whether they met him

later as postgraduate students, consultants, friends, or as fellow officers in the military service. His patients were loyal and devoted to him. They invariably appreciated his painstaking method and unusual skill as a doctor. He brought a tremendous vitality to his work. Even when very tired and in the last months when very sick he carried on with the spirit of one who found life exciting, important and full of humane interest. With all of his learning he was distinctly a man of action who found in the practice of his profession an outlet for an amazing energy that overflowed into other fields. American medicine has lost one of its most distinguished members and the American College of Physicians a great Fellow.

Dr. Truman G. Schnabel,  
1704 Pine St.,  
Philadelphia, Pa

Dr. Frank William Fleischaker (Fellow), Louisville, Ky., died November 26, 1928, at St. Joseph's In-

firmary, of heart disease following a recent surgical operation.

Dr. Fleischaker was born at Louisville, September 14, 1877. After graduation from the Louisville High School, he attended the Louisville College of Pharmacy, graduating in 1897, he then entered the University of Louisville, Medical Department, and received his medical degree in 1900. Immediately thereafter he went abroad for postgraduate medical study at the Universities of Heidelberg, Berlin and Vienna. He was professor of medicine at his alma mater from 1916 to 1925, when he became professor of clinical medicine at the same institution. This appointment he still held at the time of his death.

Dr. Fleischaker was a member of the Phi Chi medical fraternity, a member of the Jefferson County Medical Society, a member of the Kentucky State Medical Association and a Fellow of the American Medical Association. He was elected a Fellow of the American College of Physicians in 1920.

#### ANNALS OF CLINICAL MEDICINE

There is a limited stock of complete volumes and odd lots of the 1922 to 1927 volumes of *Annals of Clinical Medicine* available for sale through the Executive Secretary's office at Philadelphia. Single copies of any number, where available in broken lots, will be sent postpaid for \$50.

It is also possible to secure any particular article that appeared in these five volumes in quantity by placing an order for reprinting through the Executive Secretary's office.

#### YEAR BOOK OMISSION

The following physician was omitted in error from the list of Associates, both alphabetical and geographical.

Elkourie, Haickel A. (I), 1230-35 Martin Building, Birmingham, Alabama, born '80, M.D. University of Nashville, Medical Department, 1901, Member, Jefferson County Medical Society, Alabama State Medical Society, Southern Medical Association, American Medical Association, and an Associate of the American College of Physicians, Licensed, Alabama, Kentucky, Tennessee.

# Thirteenth Annual Clinical Session of the AMERICAN COLLEGE OF PHYSICIANS

BOSTON, MASS., APRIL 8-12, 1929



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# The Problem of Pseudo-Syphilis\*

BY JOHN H STOKES, M D , *Philadelphia, Pa*

WE are but lately come from the day when the first duty of a syphilologist was to emphasize the importance of a high degree of chronic suspicious alertness towards the omnipresence and the difficulties of recognition of syphilis. In many situations, and in certain groups and communities, that day is certainly not passed. There can be no doubt that emphasis on this aspect of the problem of diagnosis has been and still is well placed. But it is to the credit both of the revived teaching of syphilology and of the conscious effort of the practicing physician to keep abreast of the best his time affords, that the proportion of undiagnosed syphilis is probably materially on the wane. Coincidentally with this improvement in diagnostic standards there is developing the usual secondary wave of qualification and reappraisal of diagnostic methods on the one hand, and a wave of over-enthusiasm in the use of certain of them, on the other. There can be very little doubt that today as a result of wholesale application of single diagnostic procedures there is a good deal of syphilis diag-

nosed which is not syphilis at all. In some instances the difficulty is an obvious one. Error in the performance of some essential test throws the diagnostician off the track and raises suspicions which can be stilled only by the institution of treatment as a therapeutic test, if nothing more. On other occasions the extraordinary facility with which syphilis apes every disease in any field of medicine leads inevitably to a borderline of confusion in which not only one but a number of really very presentable reasons can be urged for regarding a patient as syphilitic when as a matter of fact he does not have the disease. The x-ray picture of a bone, as you shall see, the feel of a liver, nodules in a testis, an incisor tooth, may be the point on which a diagnosis seems to turn. These more genuinely complicated pictures of pseudo-syphilis form the fascinating diagnostic problems which an observer of syphilis endeavoring to apply a general knowledge of the biology of the infection is constantly obliged to confront. Perhaps it is because my practice in the last four years has offered what seems to be unusual opportunities to witness the contestable or the mistaken diagnosis of syphilis, that I feel this problem important enough for attention this evening. On the other hand, at least one competent ob-

\*Read before the Academy of Medicine and affiliated societies, Rochester, N Y, January 2, 1929. From the Department of Dermatology and Syphilology, School of Medicine, University of Pennsylvania.



server has preceded me into the field, in the person of Herbert Mitchell,<sup>1</sup> who now nearly two years ago directed attention to the importance of false laboratory reports in fastening a mistaken diagnosis of syphilis upon numbers of patients. In giving you my impressions of this genuine problem in every-day syphilology I should like to take up the matter under four heads with appropriate case illustrations, which deal (1) with the laboratory sources of error and their control, (2) the biologically false serologic report, (3) the non-specific therapeutic test, and (4) an example of the clinical story of a typical pseudo-syphilis.

*The Laboratory Sources of Error.*

It should be axiomatic that no serologic laboratory, no matter how well and conscientiously conducted, is ever always right in its positive reports. The incidence of false positiveness probably ranges somewhere between  $\frac{1}{2}$  of 1 per cent and 2 per cent in the properly controlled laboratory. Errors occur in waves and can have a tendency toward false positives or false negatives. In viewing a graph this summer at Geneva representing the accumulated experience of what is probably the most thoroughgoing comparative check of serologic procedures that has ever been made that of the Conference on Biological Standards under the auspices of the Health Organization of the League of Nations in Copenhagen last June, the proportion of false or non-specific positives obtained by some of the older Wassermann procedures, even with multiple antigens, appeared alarming and almost unbelievable. It

applied, not alone to partial positives and weak positives, which everyone today should have learned to regard with caution, but even to strongly positive serologic results. If under the relatively controlled conditions of such a comparative study, 35 per cent of the reports by a certain procedure can be non-specific, it can be readily imagined that under less controlled conditions there must be laboratories which are veritable mills of false reports, fastening suspicion of syphilitic infection right and left upon persons who do not have the disease. In my text-book presentation of this matter I insisted on a differentiation between biologic false positives and technical false positives. The technical false positive arises over and over in laboratories in which the general level of technical excellence may be high but in which it is not possible to control every single one of the innumerable details which are factors in a serologic result. The older types of Wassermann procedure are full of such possibilities of error, and even the newer, simplified and more exactly defined tests are by no means devoid of them. I have known the mere position of a rack of tubes in relation to the freezing coil in an ice-box to cause my staff a week of hard work in unravelling a series of false positives. The controls commonly employed do not have the infallibility with which the laboratory man is inclined at times to credit them. Records do at times get twisted and it does actually seem as if even so remote a thing as the woman technician's menstrual period sometimes had a definite relation to the return of a batch of anomalous and

uninterpretable results I refrain of course from mentioning the obvious sources of false results, such as dirty glass-ware, careless handling of reagents, too frequent bleeding of depleted animals, failure to control the titer of reagents, and so forth. A point I wish to insist on is that even the technically good laboratory will find constantly arising within itself one or another of these sources of error in serologic reports. Sheplai, Lyons and MacNeal<sup>2</sup> less than a month ago used the admirable phrase "serologic discord" in speaking of the astonishing range of variation in parallel tests of various kinds performed on the serum of patients with late syphilis. While there is in general a high proportion of freedom from error in any of the serologic procedures performed on early syphilis and in persons who do not have syphilis, persons who may have syphilis in its latent or later stages are subject to the full technical vicissitudes of the test.

Take as a general example of the situation with which the consultant finds himself all too frequently confronted the following:

Case 1—A man of 53 years of age whom I personally examined in March 1927 exhibited the clinical symptomatology of a very early paresis with a Kolmer blood Wassermann reaction of 32200, and a Kahn of 444, a spinal fluid of 4444 to 0.2 and 0.4 cc., a strongly positive Pandy, 5 cells and a colloidal mastic of 5555543210. Owing to some technical difficulties encountered by the home physician in treating his case, he had only a very moderate amount of treatment while

away, which could not possibly have changed his serologic reactions materially. A letter received from the physician who dealt with the technical complication and took over his case, reads as follows:

"He was suffering from an injection abscess of the buttock. We opened it and drained about three pints of sterile pus. He has made a good recovery. His blood and spinal fluid are negative. If you have any suggestions relative to future treatment I would welcome them very heartily."

Experience with the biology of the disease, that stabilizing and determining factor which I shall mention more than once again, led me to doubt the accuracy of this report on blood and fluid though I had every personal confidence in the man who quoted it. I requested that the patient see me again. He confirmed the statement that a spinal puncture had been done in the home hospital with a negative report, but I none the less insisted upon and performed a second spinal fluid examination, drawing enough to have the test completely controlled by two laboratories and checking the blood at the same time. The results were as follows:

The spinal fluid examination performed in Kolmer's laboratory and my own, simultaneously, yielded the following results respectively: Kolmer Wassermann 44300, globulin weakly positive, cells 5, gold sol 5553200000, and Kolmer Wassermann 3444, globulin negative, cells 5, mastic 5432100000. The two reports, as you see, are almost identically positive, not negative. The Kolmer Wassermann and Kahn tests

on the blood were likewise strongly positive

Imagine now the situation in which I found myself—certainly not one to endear me to the home folks, for who is less beloved than he who revealeth an error? If, accepting the report of the home physician's hospital on this patient's serology, I had proceeded to advise further in regard to his treatment without a re-examination, the patient would have gone from bad to worse. Whether the totally mistaken report of the home authority was the result of accidental transposition of specimens, or a gross and total miscarriage of technic, could only be decided by an investigation which I as a consultant could not possibly make. I was obliged instead to resort to the most devious hypothetical possibilities in explanation, such as the transient effect of a Netter's abscess, to save the face of the situation in the eyes of those concerned. This man's life literally hung on the inaccuracy of this particular report. He is now again under treatment for serologically active paresis and has had a third spinal fluid examination to confirm the positive results on the first and second.

Let me cite you another example from a number of typical ones gathered within the last two years

Case 2—A young man was sent to me with a diagnosis of syphilitic diarrhea and a report of a strongly positive blood Wassermann test said to have been performed by two laboratories simultaneously on specimens of serum drawn at the same time. It would seem that every precaution had been taken to secure the accuracy of

the result. He was placed under treatment for syphilis and grew rapidly worse instead of better. In bringing his docket of reports to me, he carried with him the originals of his Wassermann reports. From these it appeared probable that the two specimens of blood drawn simultaneously had been inadvertently sent to the same laboratory instead of two different laboratories. The referring physician insisted, and perhaps rightly, that two laboratories had both reported positive—in which case we may of course have been dealing with a biologic false positive or non-specific result. A total of five different Wassermann tests had, however, according to the reports at hand, been performed in one of the laboratories at the same time, on two blood specimens and all of them had apparently yielded positive results. The institution of treatment, of course, will leave the issue permanently unsettled. Clinically, the patient shows no evidence of syphilis, prenatal or acquired, and has no history of it, nor has my laboratory or a second serologic laboratory been able to find the slightest trace of positive tendency in any specimens of the serum drawn since that time. Again the biology of the disease is the factor which first arouses suspicion. Intestinal syphilis and syphilitic diarrhea is so rare that I have seen only one authentic and one suspicious case in half a lifetime spent in watching for it. The most thoroughgoing examination of the patient, his entire personal and historical make-up and every other detail on which a clinician would check the result of the serologic procedure, is absolutely negative. In fact, it is quite unbelievable

that he has syphilis. He has amebic diarrhea. This man was by no means the victim of diagnostic incompetence. He was examined by men of exceptional ability and his serologic tests performed in a private laboratory which has the confidence of its patrons and is under excellent medical direction. Yet I suspect something slipped and that the patient was placed in the puzzling situation in which he now rests on the basis of a non-specific or a false positive developing in five Wassermanns all done in the same laboratory at the same time.

I could go on for the full extent of my allotted time detailing to you illustrations of similar occurrences in other types of cases. The upshot of the whole matter is this: no laboratory is ever always right when it reports even a strongly positive Wassermann by numerous antigens. The laboratory may be right but the Wassermanns wrong for the patient may not have syphilis. No single positive Wassermann should ever be accepted as evidence of syphilis under any circumstances. No repeatedly positive Wassermann reaction should be accepted as evidence of syphilis on its face. It is always permissible to question any kind of serologic report and no laboratory is entitled or really wishes to be regarded as sacrosanct and above question. A careful clinical inquiry is invariably necessary whenever syphilis becomes a diagnostic possibility and the Wassermann in that inquiry takes rank as a symptom and nothing more. It may be advisable to accept it as the basis for treatment, but in doing so its debatable character must never be wholly lost sight of.

*The True Non-Specific Sources of Serologic Error.* We have been talking thus far about technical sources of error. Let us consider now for a few moments the biological, and hence more or less inevitable, sources of error in the serologic diagnosis of syphilis. In this problem I have been interested for a number of years and have had at least one unusual opportunity to follow through a life-time of anomalous Wassermann reports to the autopsy table. The conventionally accepted true non-specific blood Wassermann reactions occur or are said to occur in the following conditions:

BIOLOGICALLY FALSE OR TRUE NON-SPECIFIC  
POSITIVE BLOOD WASSERMANN  
REACTIONS<sup>3</sup>

- 1 Frambesia or yaws
- 2 Lepa
- 3 Tuberculosis
- 4 The acute exanthemata
- 5 Pneumonia, septicemia (subacute bacterial endocarditis)
- 6 Trypanosomiasis
- 7 Relapsing fever
- 8 General anesthesia
- 9 Advanced malignant cachexia, especially hepatic
- 10 Pernicious anemia
- 11 Malaria
- 12 Pregnancy
- 13 Weil's disease
- 14 Diabetes (?)
- 15 Systemic mycotic infections (?)

Of this rather large and incompletely investigated group my experience has been chiefly concerned with latent tuberculosis and with septic infections as apparently productive of false positive serologic reactions in combination with clinical pictures so confusing that a complete evaluation of the situation in the individual case

is sometimes impossible. I can perhaps best particularize by examples.

Case 3—A member of a Catholic Sisterhood, in late middle life, was under my observation for a period of six years and for a number of years preceding had had repeated strongly positive blood Wassermann reactions. These earlier tests had been performed by a standard Wassermann system with a comparatively low degree of sensitivity and responsible for the reporting of more false negatives than positives. Notwithstanding this fact, there was no question that this woman had repeated and conclusive evidence from the serologic standpoint that she had syphilis. On the other hand, the strongly positive Wassermans were interspersed from time to time with equally indubitable and complete negatives of the most unaccountable sort, bearing little or no relation to her previous treatment and little or no relation to her general condition. Unfortunately she died with the symptoms of a septic endocarditis before the Kolmer Wassermann and Kahn technics came into general use so that it is not possible to compare the results during her decade of ordinary serologic testing with any of the newer methods. The Wassermann procedure used in her case over a period of years, however, varied in no essential particulars from technics still in common use today in many private and institutional laboratories of this country. At autopsy the most thoroughgoing search for evidence of syphilis was made (excluding, however, tissue search for *Sp. pallida*) and absolutely nothing confirmatory of the existence

of the disease was found. The woman was a virgin, absolutely without clinical signs of prenatal infection and presented gross and abundant evidence of a lifetime marred by two interacting afflictions, an extensive tuberculosis of the hilus of the lung and a recent superimposed on an old vegetative endocarditis. From time to time in periods of debility the existence of the endocarditis had been suspected, but the tuberculosis had never crossed the threshold of clinical recognition and had only been included in her life record of clinical diagnoses because she developed from time to time showers of what appeared to be a cutaneous papulonecrotic tuberculid. On the basis of this case and a number of others which I saw previously I directed attention in my earlier publications on tuberculids to the true non-specific positive Wassermann as a factor of error in the diagnosis of syphilis and of tuberculosis. Of late the field of my observation has swung more towards the septic infection side of this combination. While I recognized clearcut and repeated false positive Wassermans as occurring in subacute bacterial endocarditis in the febrile patient, I have recently seen a number of cases suggesting that septic and infectious interludes with complete recoveries may in some individuals give rise to unaccountable isolated and even repeated non-specific positive Wassermann reports. As an illustration of the uncertainties introduced into a given case by this possibility—(a frank and typical illustration will be found in Figure 694 of my text)—let the following history serve

Case 4—A man of 48, whose wife is in good health and has two children and no miscarriages, lost rapidly in general condition during the month of September of the past year. In the latter part of August he had had what was thought to be gripe, with considerable fever ranging from 100 to 101°. Coincidentally with the onset of the "gripe" he developed what was thought to be a large gland or lump in the skin below the ramus of the right jaw, which lasted for a week, and which the patient thought was the beginning of a carbuncle, for he had had two previous experiences with lesions of this sort on the nape of the neck. On questioning he recalled that a barber some time during the month of July had nicked the skin in this neighborhood in shaving him, but that the nick healed promptly, no ulcer forming. There was no lesion in the mouth. His first blood Wassermann reaction was taken about a month after the onset of the decline in health and was said to have been positive in one of the larger state laboratories, the degree, however, not mentioned. A second test taken immediately was reported negative by one of the best known serologists in a private laboratory in this country. A third Wassermann done at once by the same man was reported positive. At about the time of the third positive Wassermann an eruption on the skin was noted, very mild in character, which an internist interpreted as a purpura. Massive blood cultures, Widal test, and so forth, were performed with negative results, but the blood Wassermann reaction was again strongly positive in a hospital laboratory operated without

clinical control. In the examination in which the purpuric eruption was recognized, a definite systolic murmur without cardiac enlargement was detected. Several previous examiners agree that this murmur had not been present in any previous examination. Treatment for syphilis was instituted, and although the eruption was already fading, it was noted that it disappeared completely within twenty-four hours after the first injection of neoarsphenamine. There was, however, no flare-up or Herxheimer reaction. There was no spectacular drop in fever, the patient still has occasional evening chills and runs a temperature ranging from 99.2 to 99.8 at night. There has been a slow but genuine improvement in general health with a continuance of the anti-syphilitic treatment. The blood Wassermann reaction was reported again two weeks after the sixth injection of neoarsphenamine as strongly positive by the same laboratory which had obtained the strong positive during the purpuric phase of the disease. Two weeks later, however, a third clinically controlled laboratory obtained the following results: Kolmer 11, Kahn completely negative, Hinton glycerol cholesterol completely negative, Kline slide test completely negative, thus without the intervention of any further treatment or the use of any heavy metal. Physical examination of the patient shows nothing definitely supportive of the diagnosis of syphilis. Exposure is admitted as of a number of years ago and the patient's mother had a remarkable series of miscarriages and stillbirths. The immediate question then is whether the patient's positive

Wassermann is a function of a prenatal, an early or a latent acquired syphilitic infection, perhaps flared up by intercurrent infection, or is a non-specific positive in the course of a septic dissemination of some organism through the blood stream from which the patient is now gradually recovering? The patient's wife and children are serologically negative. The patient has not had a spinal fluid examination, has no evidence of neurosyphilis, and the spinal fluid examination would be the last thing to commend while he is febrile, for fear of transplanting a possible circulating organism to his meninges. Did the hotel barber implant a syphilitic infection below his right ramus? It is possible, but it seems improbable, though the chronology cannot absolutely negate it. Was the eruption over his thorax and flanks a toxic erythema of streptococcal origin or a secondary syphilid? No one able to make a positive differentiation saw it. At the present time after an amount of treatment which might but probably would not have been responsible for a complete serologic reversal had he an active secondary syphilis, he is still strongly positive to the laboratory which read him positive in the possibly septicemic stage and totally negative even to such sensitive procedures as the Hinton and Kahn when he ought to be strongly positive had he a secondary syphilis. Has he perhaps an old latent syphilitic infection manifesting itself in fever and one of the debility crises that one occasionally sees in the latency of middle life? It is conceivable but difficult to believe. Perhaps he has an early syphilitic aortitis, which may be febrile.

Is the systolic murmur part of an endocarditis, or an aortitis, or may it have been functional associated with the fever? The murmur is still present and the fever itself has not responded with the promptitude which I at least have learned to expect in syphilitic fever at all stages of the disease when treated with the arsphenamines. The complete absence of other physical damage ascribable to syphilis at age 48 in a man who has had a latent syphilis for so long a period of years as this one has presumably run, is decidedly out of the ordinary though possible. Equally difficult to explain is the total absence of any stigma of the disease, if this be a prenatal infection. A positive Wassermann, even transient, is, moreover, a rare occurrence in a prenatal syphilis of forty-eight years' standing. With the therapeutic test exhibiting no clearcut result; the serology and the physical findings anomalous and conflicting, the problem for the consultant in such a case becomes one of extraordinary difficulty. Personally I met it by advocating a continuance of treatment appropriate to a recently acquired infection. I do not more than half believe the man has syphilis. But if he has an early syphilis or a syphilitic cardiovascular lesion as early as this, it would be a thousand times better to treat it thoroughly as such than not at all. He is accordingly tolerating very well the routine treatment of an early syphilitic infection. Whether or not he really has syphilis, I question if anyone short of autopsy will ever know.

As an illustration of the discretion which should be used in interpreting the blood Wassermann reaction in pa-

tients who are febrile, due to a possible septic focus, I cite the following

Case 5—A boy of 17 was hurried to the hospital because of symptoms suggesting an acute appendicitis. For various reasons it was thought inadvisable to operate. A blood Wassermann test, however, was taken as part of the routine examination and returned strongly positive, though the antigenic and technical distinctions are not available. It is stated that he has run bouts of fever, which subside when he goes to bed and recur whenever he endeavors to become active. The boy has been a wayward and peculiar lad in some ways and at one time at the age of 14 was away from home for a period of two weeks, during which his mother thinks it possible he may have suffered venereal exposure. Physical examination shows two small bilaterally symmetrical erosions in the mouth at the dental junction line on the mucosa, which disappeared with the first injection of potassium bismuth tartrate and which were not distinctively specific at the outset. There were one or two slight abnormalities of the osseous system, such as a heavy clavicle and slight thickening and rounding of the anterior aspect of the right tibia, but they were certainly not sufficient to establish a diagnosis of prenatal syphilitic infection. Four days following the first bismuth injection, serologic tests performed in a different laboratory, instead of confirming the strong positives obtained on two occasions while he was in bed with fever, yielded a completely negative Kolmer and a Kahn of 012, which is within the mar-

gin of non-specificity of the test. Subsequent Kolmer and Kahn tests, including an immediate repetition, were totally negative in all particulars. Never at any time has there again been a suggestion of positiveness. The mother's blood Wassermann reaction is entirely negative, and there is nothing to substantiate in the family a diagnosis of prenatal syphilitic infection. As I became better acquainted with the boy, I secured what I believe to be a true statement with reference to previous sexual exposure, and none has occurred. We are left, therefore, with a strongly positive Wassermann obtained on two occasions in a single laboratory during a period of confinement to bed with fever, as the sole evidence in favor of the diagnosis of syphilis in this boy's case. Obviously this is a rather slender peg on which to hang two years of treatment procedure and a lifetime of observation. Yet on evidence such as this it is probably safer to proceed with treatment than not to do so, serious though the inconvenience to the patient may be. In thinking of this boy's case I was irresistibly reminded of a young woman whom I observed for a period of years, who suffered from cyclic vomiting and who never could obtain other than a positive blood Wassermann test in a certain laboratory or other than a negative from any other serologist, of whom I had her visit three during the period of my study of her case. In the patient herself and in her entire familial background there was not a scintilla of evidence of syphilis.

The questions and doubts aroused in the mind of the practicing physician



by a recital such as this cannot be resolved by a categorical endorsement or condemnation of one or other type of serologic procedure. Yet you will inevitably want to know just what service the newer modifications and the precipitation tests are performing in dealing with this situation. I think, beginning with the Kolmer modification, all of them represent valuable departures from the established Wassermann technics in the direction of increased sensitivity with due regard for specificity. It is in fact in the older multiple antigen procedures with high cholesterinization that we meet the largest incidence of complexity and partial positive confusion if one can judge by the results of the Conference on Biologic Standards. Sheplar, Lyons and MacNeal have, I believe, offered a very plausible explanation of the situation when they suggest that each procedure, instead of picking out one uniformly and invariably present antigenic substance, interacts with one or another of a number of substances in the production of conflicting or variable positive results. It is highly probable that the non-specific margin of error in all of the serologic tests for syphilis today, arises out of a multiplicity of antigenic substances, some of them not highly specific in origin, which give rise to the conflicts and the dubieties which so impress, not alone the practicing physician but the consulting syphilologist.

It behooves me in rounding out my remarks on this subject to submit to you at least typical instances of the fallibility of the therapeutic test and of the clinical pseudo-syphilis which I mentioned in my introduction.

At one time in discussing the principles underlying the therapeutic test, I emphasized the fact that it should never be performed for a vague or ill-defined group of symptoms and that the non-specific margin of effect of the therapeutic agents employed in the test should be kept constantly in mind. For example, to test a patient therapeutically for syphilis because he has headache and sore throat would be the height of folly, for headache and sore throat are symptoms of innumerable ailments as well as syphilis. Similarly, to test a patient for the syphilitic nature of a macular eruption on the thorax with an arsphenamine is a fundamental mistake, for the macular eruptions most likely to simulate syphilis belong in the toxic erythema group, and toxic erythemas, to say nothing of their spontaneous involution, respond often with astounding promptness to a single injection of neoarsphenamine. You will recall that this was an important interpretative item in the case of the man with fever described above. Agents with a high degree of non-specific effect, such as potassium iodide, should never be used in the precise delineation by therapeutic test of the extent and character of a syphilitic infection. I well recall the general practitioner, who while I was still in medical school gave me the recipe for his success in practice, "If everything else fails, try a little KI, they probably have got syphilis." He made his reputation on that hunch and Heaven only knows how many people with everything ranging from psoriasis to asthma passed through the shadow of suspicion at his hands with curative results. In these days, however, it is

too serious a matter to place a patient in jeopardy of the modern anti-syphilitic therapeutic barrage on the evidence afforded by therapeutic response to something as completely non-specific as iodide. To avoid, then, still another perplexing aspect of non-specific or pseudo-syphilis, it behooves the practitioner to know before he begins a therapeutic test the margin of non-specificity of the drug he proposes to use. Even mercury has a non-specific therapeutic effect. Probably bismuth is today the most available and the least specific of the various employable drugs, yet bismuth will clear up psoriasis and lichen planus and was used within a month as proof of their impossible contentions by that irrepressible group of cranks who insist that all psoriasis is due to syphilis. Just as an illustration of the positive therapeutic test which does not illuminate the diagnosis let me cite the following case. It emphasizes an additional principle as well, that a therapeutic test directed at a non-specific lesion is as likely to give a confusing and non-specific result as if performed with a drug of low specificity for syphilis.

Case 6—A man of 59 with a propulsion gait so marked that he can scarcely totter about, a masked facies suggestive either of the most advanced Parkinsonism or the most degenerated paresis and with a hesitancy in speech that leaves one undecided as to whether he is an extreme example of multiple sclerosis or an almost completely aphasic paresis, is brought to me with a diagnosis of neurosyphilis. The blood Wassermann reaction is

negative. The spinal fluid examination, taken immediately following the seizure with which this process began, was negative to the Wassermann procedure, but was said to show a positive globulin, 10 cells and a tabetic gold sol and benzoin curves. Under mercurial inunctions the man got rapidly worse. His neurological examination by Doctor Spiller brings out the statement that a hemorrhage of the basal ganglion would give the same symptoms and findings as this man presents. Such a lesion certainly cannot be regarded as specific and a therapeutic test directed at it cannot be expected to yield other than a non-specific response. Yet within three weeks after the patient is placed on bismuth arsphenamine sulphonate he is walking without a cane, the voice previously inaudible and the speech so retarded that its rate could not exceed ten words a minute is transformed into a reasonably fluent telephone voice, and his facial mask has lost 30 per cent of its fixity. Has this man neurosyphilis and are we resolving a gumma or a vasculitis in the basal ganglion? Not a bit of it. He is simply enjoying the effect, not unfamiliar to those who know their arsphenamine, of an improvement in a Parkinsonian syndrome under this highly non-specific drug used in tonic doses.

As my final contribution to this hour of perplexities I want to offer you a typical illustration of pseudo-syphilis, meaning thereby a disease complex apparently not due to syphilis which none the less presents in its course a series of incidents, in and of themselves rarely seen elsewhere than in syphilis and yet when examined in

the light of the entire story of the case and of a knowledge of the life history of a syphilitic infection, quite obviously non-specific in character and origin. In many difficult cases the sometimes almost indefinable sense of fitness of the syphilologist who has developed an instinct through long experience, is perforce the court of last resort.

Case 7—A woman of 36, a virgin and in previous good health except for nervous disturbances, requested in April, 1926, examination for what was thought to be a urethral caruncle. Immediately upon the discovery and following menstruation, which came on at the same time, she developed what appeared to be an acute infection. The symptoms were those of a severe urethritis, the smears showing a short diplobacillus in two competent laboratories. Following the use of an enema the rectum apparently became infected with the same organism, giving rise to bleeding and pain. Cystoscopy was negative and cautery was used on the caruncle. For a week the patient was much better and then, following repetition of the cautery, pain and burning reappeared. The vagina became involved with severe pain and spasm and the examining physician states that the mucosa was "plush" all the way up into the fornices. This time the patient had fever and two days later while in bed at the hospital her menstruation appeared with a small amount of bloody discharge having an extremely fetid odor. Local treatment of the vagina, with drainage, was carried on from August to October and an eruption of some kind developed of which

no clear account can be obtained, associated with vulvar itching. Under continuance of local treatment the patient was comparatively comfortable until March, 1927, when she suddenly developed a gingivitis, followed a week later by symptoms of stiffness, swelling of the neck glands, especially on the right side, and pains in the right and then the left shoulder. A glossitis followed and a painful spot appeared in the left chest. Coincidentally a general eruption appeared which was of a florid red, itched somewhat and was accompanied by mouth lesions from which a distinct pellicle or skin could be picked. Patches were most numerous on the gums. A sole spot appeared on the head in the left frontal region with a visible swelling accompanied by fever to 101°F. The mouth lesions finally cleared up. An x-ray of the skull taken in May showed typical eburnation of the inner table of the type frequently observed in lues. Note now the serologic history.

Her blood Wassermann reaction taken at the height of the eruption was negative, a most unusual occurrence for syphilis, though possible. The next blood Wassermann reaction taken when the bone manifestations were observed, showed an anticomplementary Kolmer and strongly positive Kahn, again an unusual occurrence. There were then four or five delayed negatives, part of a provocative procedure. A spinal fluid examination was done and showed a negative Wassermann and colloidal tests but an increased cell count, apparently somewhere between 9 and 19. Diplo-organisms, not gonococci, were found in the vaginal smear. The fever continuing and the patient

definitely ill, the administration of sulpharsphenamine was begun with mercury intramuscularly, but even after six sulpharsphenamine injections and well on into the ensuing rest period, fever continued. It disappeared two weeks after the patient began injections. The vaginitis suddenly cleared up following the passage of a large clot of blood in the October menstruation, menstruation having ceased entirely during the three months of acute symptoms.

The patient is now well to all appearances and the serologic tests, both Kolmer and Kahn, are totally negative. The blood viscosity is within normal limits and low for a syphilitic patient who is carrying a false negative. The physical examination of the patient in my office, after the sequence of events above described, yields nothing to support a diagnosis of an active syphilitic infection. The x-ray plates as shown me by the examining physician do unquestionably show bone lesions involving the inner table of the skull of the vertex and frontal regions, which might pass as syphilitic in character and which showed undoubted healing change during the treatment for syphilis which was instituted. At the time of the pulmonary incident a definite small shadow about 3 cm. in diameter and roughly round in shape was observed in the lower right near one of the larger bronchi, but this has since disappeared. The patient is almost hysterical over the tragic possibilities involved in the diagnosis of syphilis and at the same time so syphilophobic as to be absolutely unreserved in all her statements in regard to her history.

Does this young woman have syphilis or does she not? Two able clinicians have told her that they believe she has and it certainly must be confessed that if one saw the x-ray plates alone or heard the patient's account of but a single phase of the situation, the conclusion would be difficult to escape. On the other hand, I believe that a comprehensive survey of the biology of the situation in the light of a knowledge of syphilis in general, justifies the belief that this young woman does not have the disease—even though she has had anti-complementary Kolmers and positive Kahns, which are usually interpreted as strongly suspicious of syphilis, and has had delayed negatives and a rise in spinal fluid cell count to accompany them. To quote from my report on the matter, "this infection, whatever it may be, has not followed a course which my experience or instinct leads me to believe is syphilitic. I believe rather that she has been the victim of a hematogenously disseminated infection of some other type, possibly of a streptococcus or diplo-organism, with invasion by way of the genital tract and the uterus during menstruation and with metastases during the acute phase to the bones of the skull, the lungs and even with a transient slight meningeal reaction. Such transient meningeal reactions in association with various banal infections are well known through the observations of Herrick. I feel that the cutaneous manifestations, though I did not see them, might well be interpreted as on the borderline between erythema multiforme and erythema nodosum and that the mucous membrane lesions as described to me are

more suggestive of this possibility than of syphilis. All things taken together, then, I do not believe that this young woman has the disease. I feel that the therapeutic response exhibited in her case was in all probability non-specific and in keeping with that seen in erythema multiforme and erythema nodosum and in the bacteremias and septic endocarditides following the administration of an arsphenamine. The question now arises as to whether treatment should be continued. On this point I feel that it is safer to recommend the continuance of antisyphilitic treatment over a reasonable period than to leave this patient's future either to the diagnostic uncertainties of the case or to the prospect of non-specific recurrence if an aberrant infection still lingers in any tissue of the body."

It would be an injustice to sponsor such a session of diagnostic uncertainties, without proposing at least some means of meeting the situation. What controls can be applied to situations such as these which will leave a firmer ground beneath our feet? In the field of control of laboratory error, it is easier to suggest methods of preventing confusion than in the field of pseudo-syphilis itself. I venture the following suggestions:

1—Never in a doubtful case accept a single serologic report from one laboratory or even two reports performed at the same time in the same laboratory, without an internal check of at least two methods and a repetition.

2—Never accept any serologic report which does not give the degree

of positiveness, the antigens and the technic.

3—Never accept a spinal fluid report which does not give the details of all four test procedures: Wassermann, globulin, cell count and colloidal tests. The bane of the consultant's existence is the incomplete spinal fluid report, whether due to too small quantity, blood contamination, shipment conditions or laboratory inadequacy.

4—Refuse any longer to accept a report based on a single type of procedure—i.e., complement fixation only, or precipitation only. For ordinary practice as well as for the expert it is not too much to require both—and 3 or 4 tests of radically different types are often helpful.

5—Never consider a laboratory report as apart from the clinical examination of the case. While the laboratory may furnish the only available evidence of syphilis, the clinical examination and the careful historical appraisal may furnish the only evidence against syphilis, entirely too often to be neglected. A Wassermann is part of a case, not a case in itself.

On the positive side I offer the following:

It is safe to say that there is only one type of laboratory which is adequately controlled from the clinical side, and that is the serologic laboratory which works in cooperation with a syphilis clinic. All other laboratories divorced from the one court of last resort are the inevitable sufferers from factors of error which they can never control or detect by any system of checks and balances within themselves.

Answerable as they are only to inexperienced practitioners and general clinicians with a limited and uncontrolled material in syphilis, their margin of error is certain to be larger and more continuously in evidence than that of a laboratory checked and accountable to a well-organized syphilologic clinic. The small private laboratory operating in two or three rooms in a skyscraper totally divorced from the world of syphilologic practice is the most dangerous source of error with reference to the diagnosis of the disease that exists today, and this statement is true almost regardless of the name and fame of its head. Even inter-laboratory checks cannot adequately control the factors of error in such organizations. They are divorced from the case. It will represent no mean advance when even the great state laboratories are obliged to check themselves continuously against one or more of the established syphilologic clinics in their regional domain.

I wish I could be as simply, and I hope as convincingly, aphoristic in my suggestions for the application of clinical criteria of decision to the patient with pseudo-syphilis as one meets him in the consulting room. The judgment exercised there has an inevitable personal and temperamental quality which is not exactly reducible to control terms. It rests upon the range and penetration of the syphilologist's insight into the life story of the most versatile of all disease simulators and the details of the most varied of pathologic panoramas. A large part of it is subconsciously stored. A balance must be drawn between impressions based on

the survey of much material and the instinctively noted landmarks of the individual patient's case. There must be a laying on of hands, *persona propria*, for in contravention of an earlier utterance of my own, something passes through the fingers and the ears and the eyes as one manipulates and searches the patient himself in personal examination, which is of the essence in critical decisions and cannot be inscribed in reports. When such an examination has been made, when complete returns of the laboratory aspects of the work-up from controllable sources are before him, let the arbiter take twenty-four hours. Long before it is up, the subconscious mind may have made the decision, and the hair of his neck may bristle like that of wolf-hound on scent. Yet let him hold himself in leash, and compel the leaping thought to take the slow, the reasoned, the tortoise pace of the written word. Instead of dashing off on an engraved card ready to hand "The diagnosis is syphilis", let him dictate one of these appalling letters, four closely written pages long in which he reveals to the horrified or bored referring practitioner, the tortures of experiential error and the pangs of logical differentiation through which he has given birth to a decision that this person has or does not have syphilis. After that, though as judge he may expose another's error uncharitably, though he may confess bafflement, though he may decide wrongly and be in later months or years reversed—he'll grow, and like the just, he will sleep well.

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# Basal Metabolism in Polycythemia Vera\*†

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**F**OLLOWING the introduction of the Zuntz Geppert method of studying the respiratory metabolism, Senator, Lommel, Tangl, Gordon, Grafe, von Bergmann and Plesch, Róver, Plehn, Mohr, and Shill reported individual cases in which such studies were made on patients with polycythemia vera Mosse (1920) collected these and presented them in convenient tabular form He expressed the data, however, in cubic centimeters of oxygen for each kilogram of body weight Grafe (1923) in his extensive monograph recalculated the data given by Mosse and stated that, in comparison with the Harris and Benedict normal standards in only six of the twenty-two cases in the literature was the basal metabolic rate increased Grafe added three carefully studied cases in which the basal metabolic rates were +42, +34, and +33 per cent, and the erythrocyte counts, 8,000,000, 10,600,00 and 7,500,000 respectively Abbott, Marsh and Isaacs each reported one case of polycythemia vera in which the basal rates were +16, +21, and +31 per cent respec-

tively Minot and Buckman found that six determinations in four cases varied between +10 and +35 per cent Brown and Giffin reported that in six cases basal rates were respectively +44, +37, +22, +9, +5, and +4 per cent Harrop reported a series of fifteen cases, in which the basal metabolic rate varied between +4 and +52 per cent He stated that in the majority of cases there seemed to be a moderately increased basal rate which was not directly related to the increase in hemoglobin or to the number of erythrocytes, and on which treatment had a variable effect, although the disease was clinically improved Du Bois stated that polycythemia vera is a condition which may be accompanied by an increase of the basal metabolic rate

This report is a study of the twenty-three cases seen at The Mayo Clinic in which the basal rate was determined at the time of admission All were definite cases of polycythemia vera, with a blood volume of 120 c c or more to each kilogram of body weight, and with the exception of three cases the spleen was palpable In these three, the rest of the clinical picture was typical of the disease Care was taken to exclude from the series cases in which the polycythemia was secon-

\*Work done in Division of Medicine and Section on Clinical Metabolism, The Mayo Clinic

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TABLE I  
RESULTS OF DETERMINATIONS IN TWENTY-THREE CASES OF POLYCYTHEMIA VERA

	Height in inches	Weight in pounds	Whole blood, cc for each 100 cc of body surface	Blood cells, cc for each 100 cc of body surface	Whole blood, cc for each square meter of body surface	Blood cells, cc for each square meter	Chief complaint	Symptoms related to vascular distention	Symptoms related to organic changes in blood forming organs	Symptoms related to disturbed metabolism	Incidental complications		
1	51	830	213	191	125	7485	4900	Pruritus	Mass in left upper quadrant	High color	Mass in left upper quadrant	Asthemia, weight loss, gastro-intestinal distress	
2	44	750	215	206	129	6640	4180	Edema of ankles		High color, slight vertigo		Asthemia, weight loss of 23 pounds with poor appetite, mild heat intolerance	Adenoma of thyroid gland
3	42	560	180	191	107	6725	3770					Weight loss of 50 pounds, with no change in appetite	
4	43	760	273	221	170	8890	6755	Weight loss of 50 pounds but appetite unchanged, bleeding gums	Bleeding gums				
5	43	890	271	222	155	6190	4270	Mass in left upper quadrant	Slight headaches	Mass in left upper quadrant		Asthemia, loss of weight, appetite fair, gastro-intestinal distress	
6	49	650	200	190	114	7010	4200	Asthemia	High color			Asthemia	
7	44	640	225	183	123	6470	4330	Asthemia, vertigo, urinary symptoms	Vertigo, paresis	Mass in left upper quadrant		Gastro-intestinal distress	
8	42	630	204	120	73	4765	2880	Gastro-intestinal distress				Vague gastro-intestinal distress	Mild diabetes, ovarian cyst
9	42	670	201	120	68	5100	2890	Vague gastro-intestinal distress				Asthemia, gastro-intestinal distress, weight loss of 20 pounds	
10	41	780	274	202	140	7890	5440	Asthemia, vomiting					

11	+20	730	255	227	150	4720	2070	Parusthesia (legs)	High color, parusthesia, headaches		
12	+20	580	211	136	82	5200	3130	Pain in legs, high color	High color	Asthma, weight loss with poor appetite	
13	+18	640		224	157	8070	5650	Edema of legs asthenia	Edema of legs, hemorrhage after extraction of teeth		
14	+16	690	233	167	119	5320	3760	Gastro-intestinal distress, pain in left upper quadrant	Headache, vertigo, scotomas	Pain in left upper quadrant	Gastro-intestinal distress
15	+13	850	294	193	139	7080	5100	Headache, gastro-intestinal distress	Vertigo, tinnitus		Blood pressure systolic 190, diastolic 140
16	+10	730		173	119	6490	4490	Vertigo	Vertigo, high color	Asthma, mild gastro-intestinal distress	
17	+9	550		140	92	5225	3400	Constricting pain in epigastrium	Loquacious, nervous, tinnitus, headache, high color		
18	+9		256	174	103	5000	2800	Asthma, loss of weight	High color	Pain in abdomen (not localized)	Heat intolerance, loss of weight, asthma
19	+8	750	242	168	97	5830	3500	Cough, hemoptysis	Nasal hemorrhage, hemoptysis, cough	Asthma, loss of weight with poor appetite	Bronchiectasis and fibrosis of lungs
20	+8	700	260	180	134	7460	5600	Asthma, renal disorder	Headache, vertigo, high color, bleeds easily from cuts, and so forth	Asthma	Adenoma of prostate gland
21	+5	660		128	77	5180	3105	Vertigo, high color	Vertigo, high color	Asthma, gastro-intestinal distress, slight loss of weight	
22	+4	840	250	211	156	8050	6100	Epigastric pain	High color, irritable	Gastro intestinal distress	Duodenal ulcer
23	+3	710	251	176	106	6165	3740	Mass in right side of abdomen, hematuria, asthma	High color	Asthma, weight loss of 10 pounds with poor appetite	Hyper-nephroma

dary, cases of leukemia and cases in which treatment had been given recently. Complicating hyperthyroidism was satisfactorily excluded in all cases except one. This was the case of a woman of seventy-four years, who presented a definite clinical picture of polycythemia, with a blood volume of 191 cc for each kilogram of body weight, and a palpable spleen. She also had an adenoma of the thyroid gland which had undergone calcification. Her basal rate was +42 per cent and it was impossible to exclude definitely a mild degree of hyperthyroidism. Harrop, in his review of the subject, was able to find reports of only two cases in which hyperthyroidism could even be suspected of being present; one of these was reported by Tyrrell and the other, by Zadak. Hyperthyroidism is therefore unusual and incidental in these cases. Other incidental complications were present in six of the cases, namely a mild grade of diabetes and ovarian cyst, essential hypertension with a systolic blood pressure of 190 and a diastolic pressure of 140, duodenal ulcer, bronchiectasis and pulmonary fibrosis, adenoma of the prostate, and hypernephroma.

The series was analyzed to determine whether there was a correlation between the basal metabolic rate, using the Du Bois standards, and the following factors: (1) the blood volume for each unit of body weight; (2) the cell volume for each unit of body weight; (3) the blood volume for each unit of body surface; (4) the cell volume for each unit of body surface; (5) the degree of concentration of the erythrocytes in the peripheral circulation as determined by the routine blood count;

(6) the concentration of hemoglobin in grams for each 100 cc, and (7) the severity, multiplicity or combination of symptoms common in the disease.

Table 1 gives the results of the various determinations in the series. The cases are arranged in the decreasing numerical values of the basal rate. It is seen that the erythrocyte count, the concentration of hemoglobin, and the blood and cell volumes for each unit of body weight and surface area do not likewise fall in an arrangement of decreasing numerical values. Furthermore, there was no semblance of a curve formed, when these factors, individually, were graphically plotted against the basal rate. This evidence, therefore, indicates that a significant correlation does not exist between the basal rate and the factors mentioned, nor with the so-called cardinal symptoms as presented in table 1.

In ten cases of this series, blood volume, basal rate, and erythrocyte determinations both before and after treatment were studied. In cases 3, 12, 14 and 20, as seen in table 2, there was no significant change in the basal rate after treatment, although there was a decided decrease in the volume of blood for each kilogram of body weight as well as in the erythrocyte count. Case 3 was treated by venesection, the others by phenylhydrazine hydrochloride. In case 2, treated with the roentgen ray and venesection, in cases 6 and 8 treated with roentgen ray, and in cases 7 and 10 treated with phenylhydrazine hydrochloride, the basal rate decreased after treatment along with the blood volume for each kilogram of body weight, and along

TABLE 2

BASAL METABOLIC RATE, BLOOD VOLUME, AND NUMBER OF ERYTHROCYTES IN TEN CASES OF POLYCYTHEMIA VERA BEFORE AND AFTER TREATMENT

Case	Type of treatment	Before treatment			After treatment		
		Blood volume, cc in each kilogram of body weight	Basal metabolic rate, per cent	Erythrocytes, millions in each cubic millimeter	Blood volume, cc in each kilogram of body weight	Basal metabolic rate, per cent	Erythrocytes, millions in each cubic millimeter
2	Roentgen ray, venesection	206	+44	7 50	144	+11	6 20
3	Venesection	191	+42	5 60	131	+40	4 90
6	Roentgen ray	190	+29	6 50	146	+20	4 80
7	Phenylhydrazine hydrochloride	183	+24	6 40	103	- 4	2 60
8	Roentgen ray	120	+22	6 30	91	- 4	5 00
10	Phenylhydrazine hydrochloride	202	+21	7 80	87	+12	2 00
12	Phenylhydrazine hydrochloride	136	+20	5 80	71	+23	3 10
14	Phenylhydrazine hydrochloride	167	+16	6 90	90	+15	2 00
15	Phenylhydrazine hydrochloride	193	+13	8 50	81	+29	3 30
20	Phenylhydrazine hydrochloride	180	+ 8	7 00	75	+ 4	

with the erythrocyte count. In case 15 the basal rate definitely rose after treatment with phenylhydrazine hydrochloride although the blood volume and erythrocyte count dropped. Thus, in five cases there was a drop in the basal metabolic rate after treatment, in one case it rose, and in four cases it was unchanged. Therefore, conclusions cannot be drawn as to the effect of treatment on the basal rate.

#### COMMENT

In this series of twenty-three cases of typical polycythemia vera the basal metabolic rates ranged between +3 and +51 per cent prior to treatment. In fifteen of the cases (65 per cent)

the rate was above the normal range. There was no evidence that the rate was dependent on, or related to, the increase in the blood and cell volume for each unit of body weight or of surface area. Moreover, the basal metabolic rate bore no relation to the concentration of hemoglobin or erythrocytes, in fact, there does not seem to be any correlation between the metabolic rate and the severity of the disease as evidenced by the general symptoms. Treatment, although it produces a reduction in the blood volumes and cell counts, had a variable effect on the basal metabolic rates.

Various factors have been suggested as the cause of the increased metabolic

rate which frequently but not invariably is found in cases of polycythemia vera. Abbott suggested an increased rate of regeneration of cells. Isaacs, on the basis of high uric acid in his case, believed that the increased rate of metabolism was due to an increase in the amount of nuclear material destroyed; the erythrocytosis accounted for the increased amount of nuclear material that was available for destruction. In the present series, the blood uric acid was determined in only five cases; in all five the basal rate was elevated, but the blood uric acid was normal. Minot and Buckman suggested that the increased rate was dependent on the abnormal blood formation and the presence of immature cells in the circulation. Grafe suggested, but did not subscribe to the belief, that deranged protein metabolism, or abnormal physiologic activity of the spleen and bone marrow might be factors. That an increased blood volume might cause the increased metabolism has been advanced as a theory. Delchef in 1906 experimentally transferred large amounts of blood into dogs, but believed that the increased metabolism was due to the excitability

of the animals. This has also been the experience of other observers, so that the evidence for the theory is inconclusive. There is evidently no experimental or clinical proof satisfactory to support any of these theories, and the true cause of the increased production of heat is still a matter of conjecture.

### SUMMARY

In a series of twenty-three cases of polycythemia vera, fifteen patients (65 per cent) had an increase in the basal metabolic rate above the normal range of  $\pm 10$  per cent. An increased production of heat is a frequent, but by no means an invariable, phenomenon.

There is no relation in this series between the basal metabolic rate and the increase in the blood volume, the cell volume, the erythrocyte count, or the concentration of hemoglobin. Furthermore there is no relation between the basal metabolic rate and the syndrome of polycythemia.

The effect of treatment on the basal metabolic rate is variable.

The cause for this tendency toward increased production of heat in this disease is unknown.

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# Hematologic Study of Three Generations of a White Family Showing Elliptical Erythrocytes\*

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UNDER normal circumstances the morphology of the red blood corpuscles is so uniform that any deviation is looked upon as evidence of a pathologic state. Everyone is familiar with the striking variations in the size and shape of the erythrocytes in pernicious and severe secondary anemias in which a wide variety of abnormal red cells may be seen but without the predominance of any one form. This is not true for all blood disturbances, however, for instances are recorded in the literature in which there have been observed quite characteristic variations in the shape of the erythrocytes with a preponderance of one type of abnormal cell. In this category belongs sickle cell anemia and the more rarely observed instances of elliptical erythrocytes in the blood of normal persons. In these blood disturbances heredity is apparently an important factor.

The condition now known as sickle cell anemia was first described by Herrick (1) in 1910. A year later Wash-

burn (2) recorded the second instance, also in a negro

(2) Washburn, R. E., Peculiar Elongated and Sickle-Shaped Red Blood Corpuscles in a Case of Severe Anemia. *Virginia M. (Semi-Month.)* 15:490, 1911

Cook and Meyer (3) who reported

(3) Cook, Jerome E. and Meyer, Jerome, Severe Anemia with Remarkable Elongated and Sickle-Shaped Red Blood Cells and Chronic Leg Ulcer. *Arch Int Med* 16:644, 1915

the third case in 1915 were the first to point out its familial nature. Emmel (4) studied the blood from the

(4) Emmel, Victor E., A Study of the Erythrocytes in a Case of Severe Anemia with Elongated and Sickle-Shaped Red Blood Corpuscles. *Arch Int Med* 20:586, 1917.

father of Cook and Meyer's patient and noted latent sickling of his erythrocytes. Mason (5) reporting the

(5) Mason, V. R., Sickle Cell Anemia. *J A M A*, 79:1318, (October 14) 1922

next instance in 1922 was the first to

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call the disease "sickle cell anemia" and to suggest its racial selectivity. With the publication of the work of Sydenstricker, Mulherin and Houseal (6) and of Huck (7) in 1923 came

- (6) Sydenstricker, V P, Mulherin, W A, and Houseal, R W, Sickle Cell Anemia, Report of Two Cases in Children with Necropsy in one Case *Am J Dis Child* 26 132, (Aug) 1923
- (7) Huck, John G, Sickle Cell Anemia *Bull Johns Hopkins Hosp* 34 335, (Oct) 1923

the first real understanding of this unusual type of anemia. Their investigations showed that the anemic syndrome characterized by sickling of the erythrocytes is relatively common and not as previously supposed, a medical curiosity. Both demonstrated its constant familial character and apparent limitation to the black race. Their studies further indicated that sickle cell anemia is a definite clinical entity characterized by a clear-cut symptom-complex and by specific blood findings and anatomic changes. Since the appearance of the work of Sydenstricker and Huck many investigators have become interested in the disease as evidenced by the increasing number of reports in the literature of each succeeding year.

In negroes the sickling tendency is not rare. Mulherin and Houseal (8)

- (8) Mulherin, W A, and Houseal, R W, Sickle Cell Anemia from a Pediatric point of view *Tr Sect Dis Child, A M A*, p 77, 1924

state that Sydenstricker in a study of 1000 negroes found sickle cells in 0.6 per cent, while in an equal number of whites the anomaly was never observed. More recent investigators re-

port a much higher incidence. Cooley and Lee (9) observed sickling in 7.5

- (9) Cooley, Thomas B and Lee, Pearl, The Sickle Cell Phenomenon *Am J Dis Child* 32 334, (Sept) 1926

per cent of 400 negroes, Graham and McCarty (10) in 7.2 per cent of 608

- (10) Graham, George S and McCarty, Sarah H, Notes on Sickle Cell Anemia, *J Lab and Clin Med* 12 536, (March) 1927

colored persons and Miyamoto and Koib (11) in 19 of 300 negroes (6.3

- (11) Miyamoto, Kazuo, and Korb, J H, Meniscocytosis (Latent Sickle Cell Anemia) Its Incidence in St Louis South, *M J* 20 912 (Dec) 1927

per cent). The last named authors found no abnormal cells in 100 white controls.

Much rarer are reports of elliptical red blood cells in both white and colored people. The first recorded instance of this anomaly is that of Dresbach (12) in 1904. His subject was a

- (12) Dresbach, Melvin, *Science*, 19 471, 1904

healthy mulatto male 22 years of age in whom 90 per cent of the red blood cells were elliptical in outline. The corpuscles averaged  $4.1 \mu$  in width,  $10.3 \mu$  in length and  $2 \mu$  in thickness, with a ratio of width to length of 1:2.5. No family history was obtainable. A brother of the patient had normal erythrocytes. Dresbach and others who examined the blood believed that the condition was probably congenital in nature. In 1914 Bishop (13) reported a similar case. His patient was a man (color not stated),



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UNDER normal circumstances the morphology of the red blood corpuscles is so uniform that any deviation is looked upon as evidence of a pathologic state. Everyone is familiar with the striking variations in the size and shape of the erythrocytes in pernicious and severe secondary anemias in which a wide variety of abnormal red cells may be seen but without the predominance of any one form. This is not true for all blood disturbances, however, for instances are recorded in the literature in which there have been observed quite characteristic variations in the shape of the erythrocytes with a preponderance of one type of abnormal cell. In this category belongs sickle cell anemia and the more rarely observed instances of elliptical erythrocytes in the blood of normal persons. In these blood disturbances heredity is apparently an important factor.

and Sickle-Shaped Red Blood Corpuscles in a Case of Severe Anemia  
*Arch Int Med* 6:517, 1910

burn (2) recorded the second instance, also in a negro

(2) Washburn, R. E., Peculiar Elongated and Sickle-Shaped Red Blood Corpuscles in a Case of Severe Anemia  
*Virginia M (Semi-Month)* 15:490, 1911

Cook and Meyer (3) who reported

(3) Cook, Jerome E. and Meyer, Jerome, Severe Anemia with Remarkable Elongated and Sickle-Shaped Red Blood Cells and Chronic Leg Ulcer. *Arch Int Med* 16:644, 1915

the third case in 1915 were the first to point out its familial nature. Emmel (4) studied the blood from the

(4) Emmel, Victor E., A Study of the Erythrocytes in a Case of Severe Anemia with Elongated and Sickle-Shaped Red Blood Corpuscles. *Arch Int. Med* 20: 386, 1917

call the disease "sickle cell anemia" and to suggest its racial selectivity. With the publication of the work of Sydenstricker, Mulherin and Houseal (6) and of Huck (7) in 1923 came

- (6) Sydenstricker, V P, Mulherin, W A, and Houseal, R W, Sickle Cell Anemia, Report of Two Cases in Children with Necropsy in one Case Am J Dis Child 26 132, (Aug) 1923
- (7) Huck, John G, Sickle Cell Anemia Bull Johns Hopkins Hosp 34 335, (Oct) 1923

the first real understanding of this unusual type of anemia. Their investigations showed that the anemic syndrome characterized by sickling of the erythrocytes is relatively common and not, as previously supposed, a medical curiosity. Both demonstrated its constant familial character and apparent limitation to the black race. Their studies further indicated that sickle cell anemia is a definite clinical entity characterized by a clear-cut symptom-complex and by specific blood findings and anatomic changes. Since the appearance of the work of Sydenstricker and Huck many investigators have become interested in the disease as evidenced by the increasing number of reports in the literature of each succeeding year.

In negroes the sickling tendency is not rare. Mulherin and Houseal (8)

- (8) Mulherin, W A, and Houseal, R W, Sickle Cell Anemia from a Pediatric point of view Tr Sect Dis Child, A M A, p 77, 1924

state that Sydenstricker in a study of 1000 negroes found sickle cells in 0.6 per cent, while in an equal number of whites the anomaly was never observed. More recent investigators re-

port a much higher incidence. Cooley and Lee (9) observed sickling in 7.5

- (9) Cooley, Thomas B and Lee, Pearl, The Sickle Cell Phenomenon Am J Dis Child 32 334, (Sept) 1926

per cent of 400 negroes, Graham and McCarty (10) in 7.2 per cent of 608

- (10) Graham, George S and McCarty, Sarah H, Notes on Sickle Cell Anemia, J Lab and Clin Med 12 536, (March) 1927

colored persons and Miyamoto and Korb (11) in 19 of 300 negroes (6.3

- (11) Miyamoto, Kazuo, and Korb, J H, Meniscocytosis (Latent Sickle Cell Anemia) Its Incidence in St Louis South, M J 20 912, (Dec) 1927

per cent). The last named authors found no abnormal cells in 100 white controls.

Much rarer are reports of elliptical red blood cells in both white and colored people. The first recorded instance of this anomaly is that of Dresbach (12) in 1904. His subject was a

- (12) Dresbach, Melvin, Science, 19 471, 1904

healthy mulatto male 22 years of age in whom 90 per cent of the red blood cells were elliptical in outline. The corpuscles averaged  $4.1 \mu$  in width,  $10.3 \mu$  in length and  $2 \mu$  in thickness, with a ratio of width to length of 1:2.5. No family history was obtainable. A brother of the patient had normal erythrocytes. Dresbach and others who examined the blood believed that the condition was probably congenital in nature. In 1914 Bishop (13) reported a similar case. His patient was a man (color not stated),

- (13) Bishop, F Warner, Elliptical Human Erythrocytes Arch Int Med 14 388, 1914.

41 years of age, suffering from acute appendicitis. Routine examination of the blood revealed a polymorphonuclear leukocytosis, 5,400,000 red cells and 110 percent hemoglobin (Fleischl-Meischer). In stained smears there were many elliptical erythrocytes and repeated examinations over a period of several months showed that 75 to 80 percent were elliptical or distinctly elongated. Most of the elliptical cells measured about 130 by 50 microns. The possibility of mechanical distortion of the corpuscles was considered and eliminated. Suspecting that the abnormality might be hereditary, Bishop studied the blood of all available relatives of the patient consisting of the father, two sisters, and two nephews. Of these one sister, also in good health, exhibited the same blood picture. Bishop regarded this as strong evidence in favor of the condition being a congenital anatomical defect. More recently Huck and Bigelow (14) have described a poikilocy-

- (14) Huck, John G. and Bigelow, Rena M., Poikilocytosis in Otherwise Normal Human Blood (Elliptical Human Erythrocytes) Bull Johns Hopkins Hosp 34 50 (No. 1) 1923.

varied from  $12 \times 5 \mu$  in the fresh preparations to  $10 \times 4 \mu$  in smears. The hemoglobin percentage, red and white cell counts and platelet counts were normal. A study of fourteen members of the subject's family distributed over four generations disclosed a similar condition in her mother. The authors feel that hereditary transmission, while not definitely established, is strongly suggestive. Huck and Bigelow were able to demonstrate that this was not an instance of sickle cell anemia since the abnormal corpuscles neither increased in number nor changed in form on standing as invariably occurs in sickle cell anemia. On the contrary the cells remained in the same state in which they were first observed until the preparations deteriorated. In Huck's experience with sickle cell anemia, in which more than 50 per cent of the corpuscles acquired bizarre forms on standing, there was an associated secondary anemia which was entirely lacking in this subject although 80 per cent of her cells were abnormal. Their observations show that such a poikilocytosis differs from sickle cell anemia in every respect save the hereditary factor apparently common to both.

Lawrence (15) has reported the

by Dresbach, Bishop, Huck and Bigalow and ourselves. His patient was a woman 32 years of age who came to the hospital complaining of disability in walking. She gave a history of soreness of the mouth, bleeding about the teeth for several years, bleeding hemorrhoids for five years and profuse menses lasting from seven to nine days. She was the mother of three children, two of whom were living. Her present illness began ten months before admission to the hospital with a respiratory infection which she thought was influenza, following which she had been tired and weak. The patient appeared pale and undernourished with a slight pallor of the mucous membranes. The erythrocyte count was 3,850,000, hemoglobin 45 per cent (Sahli) and white cells 8,900. In stained smears there was a moderate achromia with rare polychromatophilic cells. Most striking was the decided tendency of the erythrocytes toward sausage forms. The platelets were apparently normal as was the differential white count. In a fresh sealed preparation examined one hour after it was taken most of the erythrocytes were observed to be fairly uniform in size with only a few small and no very large forms. From 5 to 10 per cent of the corpuscles were definitely sickle or sausage-shaped, some showing blunt or rounded ends while others were pointed. On many of the abnormal cells were slender processes from 1 to 10 micra in length which appeared to be attached to the membrane of the cells. In the crescent forms the processes were more marked and often free in the plasma. Rod-

shaped bodies thought to be broken-off processes of the abnormal red cells were observed in many leukocytes. No nucleated red cells or myelocytes were found. A brother, one sister and a niece of the patient exhibited the same abnormality of the erythrocytes. Unfortunately ignorance and superstition on the part of the family made impossible any further study of either the patient or her relatives. In a control series of 102 normal white adults sickle-shaped, sausage and filamentous red cells were found three times. In addition evidence of sickling was noted in 6 adult whites and 4 colored adults suffering from various diseases. Definite evidence of latent sickling was lacking in the white subjects but was present in the negroes. Lawrence is uncertain as to the diagnosis of sickle cell anemia in the white woman because no proof of negro blood could be obtained.

#### AUTHOR'S OBSERVATIONS

The family studied consists of Mr and Mrs A K1, their eight children and six grandchildren (Chart 1). With the exception of one daughter (Adriana) living in Portland all reside near Missoula, Montana. The distance separating the two cities has made impossible a detailed study of any member except the above mentioned daughter, although one of us (W C H) visited the remainder of the family and from the father, whose blood exhibited the presence of abnormal erythrocytes, obtained the following family history.

So far as known both parents are of pure Dutch stock. There has been no intermarriage with persons from

the Dutch colonies and prior to the emigration of Mr and Mrs K1 to America none of the family had ever been outside the boundaries of Holland. For generations the men were farmers and lived in the village of Zevenhuizen near Amsterdam. The father knew both his paternal and maternal grandparents and recalls nothing unusual in their color or facial characteristics. On his mother's side a number of aunts and uncles died from unknown causes before reaching middle age. His mother died at 40 from childbirth, his father at 75 from "old age." Two brothers and two sisters are alive and well.

Both M K and his wife enjoy excellent health and neither has ever been seriously ill. In appearance the parents are decidedly Teutonic as are also most of their children and grandchildren. All are fair skinned and exhibit none of the facial characteristics of the black race.

The only member having outspoken symptoms of anemia is Adriana whose residence in Portland has enabled us to make repeated blood examinations over a period of several months. She gives the following personal history:

Adriana N. Age 25 Married  
Registered Nurse

In childhood she had measles, whooping cough, bronchopneumonia and an attack of arthritis involving the ankle joints. Following this she enjoyed good health but was never robust. In 1918 she had a severe attack of influenza and since then has always felt weak. Upon admittance to a nurses training school in 1920 it was found that she was anemic, the hemoglobin at that time being only 60 per cent. She was allowed to enter training, however, and although anemic and always "tired out", finished in the usual three years. In 1923 while employed in the laboratory of a Portland hospital a blood examination revealed 3,000,000 red cells with 69 per cent hemoglobin (Dare). The technician who examined the blood noted the presence of abnormally shaped erythrocytes but no further investigation was made at that time.

Prior to tonsillectomy in 1923 the patient suffered from recurrent attacks of tonsillitis. For the past three years she had had bilateral maxillary sinusitis. Two years ago a pychitis developed which did not clear up for nearly a year.

For a long time she has experienced intermittent attacks of severe pain in the left hypochondrium and gastric distress described as "bilious attacks."

Menstruation began at 20 and was irregular until after marriage two years ago. The periods now occur every 28 days, usually lasting 4 days. As a rule the flow is not excessive. There have been no pregnancies.

Pelvic complete retroversion of uterus, adnexa negative.

Reflexes all are present but are quite sluggish.

Blood pressure 118 systolic, 70 diastolic.

Temperature 98.6° F

#### PRESENT HISTORY

Our attention was first drawn to the case in October, 1927, when one of us (W. C. H.) was asked to examine the differential smear of the patient's blood. At this time (Oct. 3) Mrs. N. was able to work although she felt tired and weak and appeared distinctly anemic.

#### PHYSICAL EXAMINATION

(Dr. Karl P. Moran)

October 21, 1927

The patient is well developed and well nourished. There is a distinct cutaneous pallor.

Eyes sclerae clear, conjunctivae pale, pupils react to light and accommodation.

Ears and nose negative.

Mouth mucous membrane pale, several devitalized teeth, tonsils absent, pharynx negative.

Neck anterior cervical lymph nodes slightly enlarged, thyroid palpable but is soft and not nodular.

Thorax heart and lungs normal.

Abdomen area of liver dullness is within normal limits, slight tenderness over gall bladder region, outlines of spleen cannot be percussed or palpated.

Extremities old scar 1.5 by 2.5 cms on medial surface of right calf, no palpable enlargement of axillary or epitrochlear lymph nodes.

#### HEMATOLOGIC FINDINGS

Examination of stained smears of Mrs. N.'s blood revealed a striking abnormality in the shape of the corpuscles with distinctly elliptical or oval forms predominating. Less numerous were much elongated rod-like or curved sausage-like forms and pear-shaped, sickle-like and other irregularly shaped poikilocytes, often having one or more thin filamentous processes with knob-like ends. Only a small percentage were round. Repeated counts of one thousand cells gave the following average percentage of the different varieties: oval 84.0%, round 6.7%, elongated 5.8%, irregular processed forms 4.5% (See Chart II). Achromia was lacking but some cells exhibited polychromatophilia.

Sealed fresh preparations of the whole blood under number O cover glasses, were set up, left at room temperature and examined immediately and at frequent intervals until the erythrocytes disappeared, usually within four to seven days. In these preparations the oval form was approximately 10 per cent less than in stained smears while the elongated cells were proportionately increased. Other varieties showed less variation. (See Chart II). The figures are based on daily counts of one thousand cells made over a period of a week, using the same prep-

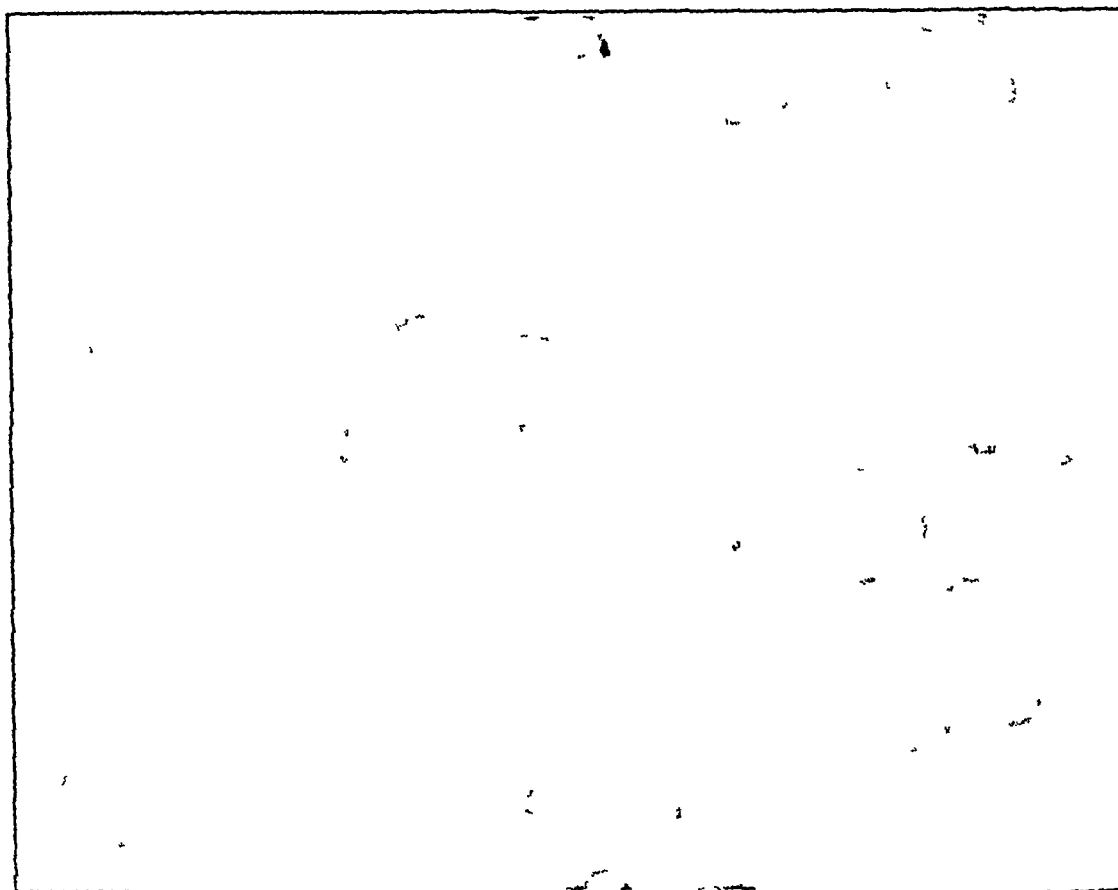


FIG. 1. High power microphotograph from sealed fresh preparation of blood of Adriana N. In this field elliptical shaped erythrocytes predominate.

ation and as nearly as possible the same portions of the slide. The lack of any appreciable morphological change definitely ruled out the possibility of sickle cell anemia. At times the long filamentous processes were seen to break off and move about freely in the serum. The abnormality of the corpuscles persisted in specimens stored in physiological salt solution and exposed in the patient's serum at 37° C. from individuals

temperature of 54° C. all erythrocytes in fresh preparations assumed the discoid form within thirty minutes.

On two occasions the fragility test showed hemolysis beginning at 0.15 and complete at 0.36. Both the qualitative and quantitative van den Bergh tests have been repeatedly negative. Blood cultures have failed to show a growth of bacteria. Further details of the blood findings will be found in Chart III.

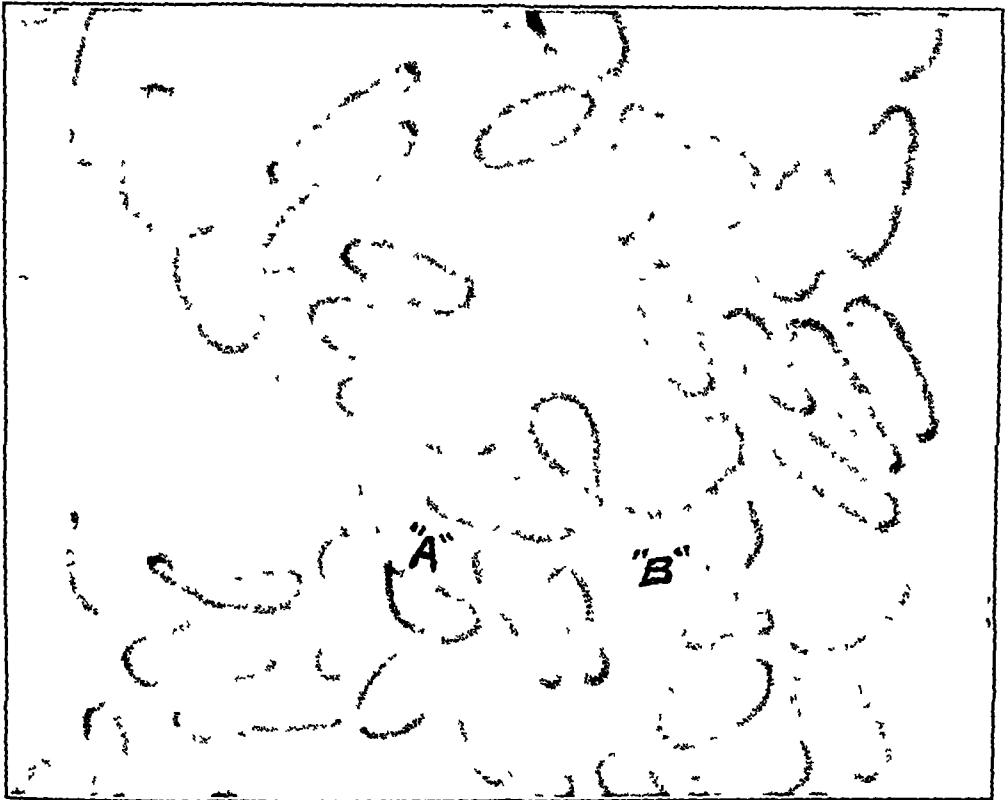


FIG 2 Another field from the same slide as Figure 1 In this area elongated erythrocytes are particularly numerous At "A" is a corpuscle showing a long filamentous process "B" is an unusually irregular poikilocyte

- (16) Larsell, Olof, Jones, N W, Phillips, B I, and Nokes, H T, The Hematopoietic Effect of Nuclear Extractives in Anemia J A M A 90 75, (Jan 14) 1928

the treatment of anemias with the nuclear extractives of liver made us anxious to try this form of therapy, especially when we found that liver had not been used in the treatment of any of the reported cases of such blood disturbances The nuclear extractives prepared in Dr Larsell's laboratory are put up in 0.5 gm capsules, six of which represent the nuclear material from one-half pound of liver From the beginning the patient has taken, except for rest periods of a week or

two, two capsules tid The results, while not as striking as in secondary anemias, have been encouraging The hemoglobin has increased from 62 to 80 per cent and the erythrocyte count from 3,750,000 to 4,560,000 Subjective improvement has been out of all proportion to that in the blood picture While under treatment the patient has carried on her household and nursing duties, gained 12 pounds in weight and at present (April, 1928) feels stronger than she has for years As the anemia decreased the gastrointestinal symptoms entirely disappeared and have not recurred The pallor of the skin and mucous membranes is much less marked than formerly



Only brief mention need be made of the blood and physical examinations of the remaining members of the patient's family.

Chart I shows the incidence of the abnormality in the entire family group. It is rather remarkable that all members of the second generation exhibit varying degrees of the anomaly. The diagnosis was made by setting up sealed fresh preparations of the blood from each individual and examining the slides at intervals over a period of 4 days. The erythrocyte count and hemoglobin are lower (Chart IV) than might be expected at the altitude of Missoula (3223 feet). However, with the exception of Johanna S. and William K1, none of the family have symptoms of anemia. All others appear strong and healthy. Because of the limited time at our disposal physical examination was not done. Discoloration of the sclerae was carefully looked for but was not observed. None of the family give a history of leg ulcer.

Huck's subjects enjoyed good health and their blood was normal in every respect except for the abnormality of the erythrocytes. In our family the red cell counts and hemoglobin figures are generally low in spite of the apparent good health of the subjects. The one member whom we had the opportunity of studying carefully had a distinct anemia without a demonstrable cause. The role of the erythrocytic anomaly as a cause of the anemia is problematical, but the low red cell count and hemoglobin shown by so many of the group who were in apparent good health suggests the possibility of some hematopoietic disturbance.

A striking similarity exists between case L. B. S., described by Lawrence, and our patient, Mrs. A. N. His description and microphotographs of the blood are almost identical with the findings in our patient. His patient also had a secondary anemia but with more obvious causes than ours.

During the course of the study we

# Elliptical Erythrocytes

CHART I  
OCCURRENCE OF ELLIPTICAL CELLS IN THREE GENERATIONS OF A WHITE FAMILY

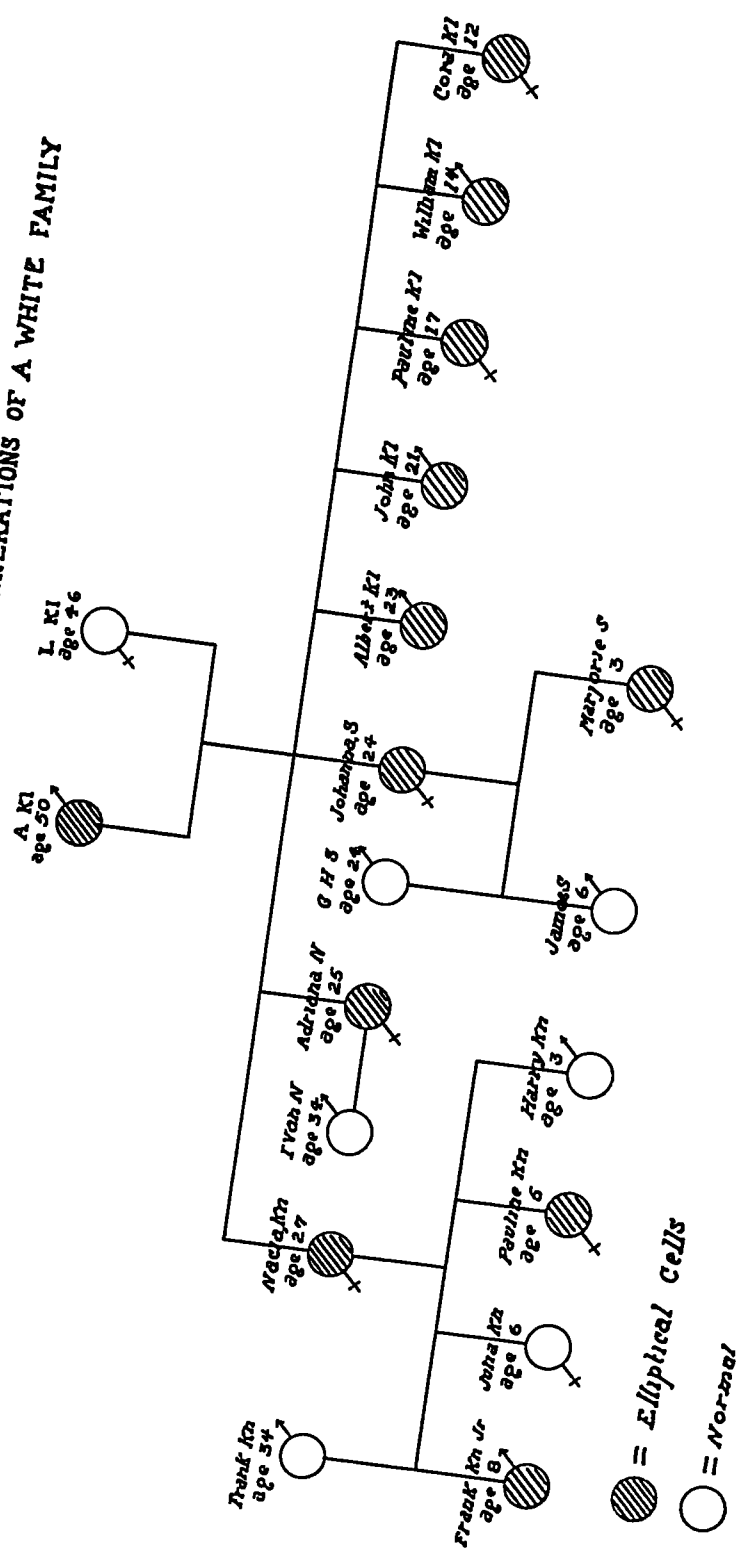


TABLE II

Shape of corpuscles	Stained smears	Fresh Preparations	Average dimensions of cells
Round	6.7%	2.1—11%	9 $\mu$
Oval	8.0%	72.1—76.8%	7 $\mu$ $\times$ 11 $\mu$
Elongated	5.8%	10.0—21.2%	18 $\mu$ $\times$ 13.4 $\mu$
Procesed (irregular)	4.5%	1.9—7.3%	Variability too great to give average figures

Types of erythrocytes occurring in the blood of Adriani N

- (17) Hahn, E. Vernon, and Gillespie, Elizabeth B., Sickle Cell Anemia Report of a Case Greatly Improved by Splenectomy Experimental Study of Sickle Cell Formation Arch Int Med 39 233, (Feb) 1927

negro's erythrocytes sickled rapidly under the influence of carbon dioxide gas and reassumed the discoid form when oxygen was passed into the chamber. Such a change was lacking in the blood of the white patient. On passing carbon dioxide into the chamber a few cells became bilobed but nothing further developed.

The condition is apparently identical with the elliptical cell anomaly in negroes and whites described by Dresbach, Bishop and Huck and Bigalow. We are in full agreement with Huck and Bigalow that this condition may be differentiated from sickle cell anemia by the fact that the corpuscles are abnormal in outline on immediate examination and do not require a time interval for development as in sickle cell anemia. Careful counts over a period of several days have failed to disclose any appreciable change in the form or number of abnormal erythrocytes.

## SUMMARY

1. A rare familial and hereditary abnormality of the red blood cells occurring in members of three generations of a white family is described.
2. The abnormality is characterized by the presence of elliptical, elongated and irregular shaped erythrocytes present in the circulating blood of the affected individuals. In sealed fresh preparations of the blood no time interval is required for the development of the abnormal forms nor do these increase in number or show alteration in shape on standing as occurs in sickle cell anemia.
3. In contrast with two previously reported studies of this kind several of our subjects were more or less anemic.
4. One member of the family having well marked anemia and treated exclusively with the nuclear extractives of liver has shown an appreciable improvement in the hematological and clinical picture.

## 1173

Date	10/6/27	10/10/27	10/23/27	11/12/27	12/12/27	1/6/28	2/22/28	3/22/28
IIb (Sahl)	62%	63%	65%	71%	76%	79%	68%	80%
RBC	3,750,000	3,850,000	3,935,000	4,016,000	4,350,000	4,480,000	3,500,000	4,560,000
C I	0.8	0.79	0.76	0.85	0.83	0.86	0.94	0.86
Anisocytosis	Moderate	Moderate	Moderate	Moderate	Slight	Slight	Moderate	Slight
Poikilocytosis	Marked	Marked	Marked	Marked	Marked	Marked	Marked	Marked
Nuc RBC	1 Normo-blast	1 Normo-blast	1 Normo-blast	none	none	none	none	none
WBC		9,400	5,600	8,400	14,400	11,400	5,100	8,400
PMN	78%	62%	69%	66%	76%	2%	67%	72%
PME	1%	1%	0%	0%	0%	0%	0%	1%
PMB	0%	0%	0%	0%	0%	0%	0%	0%
L Lymphs	2%	1%	2%	3%	2%	2%	2%	1%
S Lymphs	16%	1%	2%	3%	2%	2%	2%	1%
Other WBC	none	none	29%	30%	20%	20%	26%	24%
Trans	3%	5%	none	none	none	none	5%	none
Remarks	Before treatment	Treatment started	Under treatment	Under treatment	Under treatment	Under treatment	Menor-rhagia	Under treatment

## CHART IV

Name	Sex	Age	Date	R B C	Hb Sahli	Abnormal R B C	Leuko-cytes
A Kl	M	50	10/30/27	4,118,000	96%	Many rod, oat and sickle-like forms	6,840
Mrs L Kl	F	46	10/30/27	5,514,000	108%	none	9,200
Nacia Kn	F	27	10/30/27	3,760,000	81%	Few rod and sickle-like cells	8,860
Johanna S	F	24	10/30/27	3,304,000	85%	" "	7,700
Albert Kl	M	23	10/30/27	4,280,000	94%	" "	6,620
John Kl	M	21	10/30/27	4,224,000	81%	" "	10,400
Pauline Kl	F	17	10/30/27	2,936,000	79%	Many elongated, pear-shaped and sickle cells	8,800
William Kl	M	14	10/30/27	3,056,000	74%	" "	7,900
Cora Kl	F	2	10/30/27	3,320,000	83%	" "	11,600
Frank Kn Jr	M	8	10/31/27	3,900,000	85%	Few elliptical and rod forms	9,700
Julia Kn	F	6	10/31/27			none	
Pauline Kn.	F	5	10/31/27	4,600,000	86%	Very few oval and rod-like cells	
Harry Kn	M	3	10/31/27			none	
James S	M	6	10/31/27			none	
Marjorie S	F	3	10/31/27	4,640,000	96%	Few oval cells	15,200

# Potassium Permanganate in the Treatment of Pneumonia

By JOHN L. CHESTER, *Detroit, Mich*

THE potassium permanganate treatment of certain diseases of toxic and infectious origin first came to my attention in a purely accidental manner. A professional colleague inadvertently mentioned that this oxidizing antiseptic and deodorant, held in aqueous solution and slowly injected into the rectum as a retained enema, had been reported from England as productive of startling results in pneumonia. I do not know that I gave much heed to the reported discovery at the time, if such a discovery there was. Like most practitioners I had become somewhat immune to enthusiasm over 'discoveries' of pneumonia specifics. Too many of them had been all too frankly disappointing. At any rate, I was then unfamiliar with the available literature on the subject, although conscious of the potency of potassium permanganate salt as an antidote in certain cases of poisoning.

In the early part of 1928, at Providence Hospital I was called in consultation on an advanced and seemingly hopeless case of flu-pneumonia, which was later suggested by x-ray examination to be of tuberculous origin. The patient a highly cultured gentleman of middle age had been under treatment for six days and was then

in a pneumonia jacket and practically moribund. He was verging on extremis, and was markedly cyanosed, moaned considerably, coughed with great difficulty, and at intervals expectorated quantities of rusty colored sputum. There was a weak, thready pulse, abdominal distension, and bubbling, coarse râles heard in apices. The temperature was 102.2, pulse rate 115, respiration 40.

All known methods of treatment seemed to have been used in this case, without producing a scintilla of evidence on which to base a favorable prognosis. The moment had arrived for heroic measures. It occurred to us that whatever the merits of the now-recalled potassium permanganate treatment, it might justifiably be attempted here as a last resort.

## HISTORY OF THE TREATMENT

Hurried search of The Practical Medical Series (General Medicine), of 1927, while revealing somewhat meager confirmatory evidence, instanced (The British Medical Journal of March 7th, 1925) interesting experiments made under the direction of a general practitioner in the North of England. Dr Herbert W. Vout of Birkenhead therein reported a series

of cases of toxic origin, which had shown gratifying improvement after being treated with a standard solution of this agent, single and in conjunction with thyroid extracts

In March, 1924, the first case of pneumonia had been successfully treated by this method. A youth, aged 16½ years, a moderately severe case, with extensive involvement of the left lung, received half a pint of the standard solution twice daily for eight days. In a matter of hours the temperature was reported to have dropped two degrees F, expectoration was being coughed up more readily and rapidly lessened, and a greater degree of relief progressively experienced. The temperature had become normal in thirty-six hours. Convalescence eventuating, it was reported more rapid and less exhaustive than is usually observed under similar conditions treated by more orthodox methods.

Another English practitioner, Dr Nelson J Roche of Southsea, cognizant of and impressed with Dr Nott's original experiments, had embraced the opportunity, in a measles epidemic in his immediate neighborhood, to test the value of this method of treatment. The results of the exposition of the solution at his hands are to be noted in *The British Medical Journal* of March 12th, 1927.

Selecting five juvenile cases, complicated with well developed signs of broncho and lobar pneumonia, Dr Roche's procedure, also using the standard solution, was approximately as follows: he gave 3 ounces every 3 hours for the first 12 hours, 3 ounces every 4 hours during the next 24

hours, 3 ounces every 6 hours for the following 3 days, 3 ounces every 12 hours for the final 4 days. Improvement was invariably noted within 24 hours, and in 48 hours, the changes were remarkably progressive. Respiration and pulse rate immediately slowed, temperature fell, restlessness abated, color improved, sleep became normal, cough became less frequent, and the patients were able to raise expectoration with comfort and ease, the sputum rapidly losing its rusty color. Within 6 to 8 days, Dr Roche's cases assumed normal proportions symptomatically, convalescence being rapid and uneventful in every instance.

#### OUR FIRST CASE

These English cases suggested that this single agent might have a true specific action on the micro-organisms of pneumonia as exemplified in our case, and we decided to put the treatment to the question. We used the standard solution,—two grains of permanganate to one and one-half pints of warm sterile water, injected rectally by means of a funnel and catheter, the patient lying on his left side, and with the intention of the fluid being retained.

The initial injection was 4 ounces, repeated every 3 hours. Within 12 hours the patient began to show some signs of improvement in a dropping of temperature, pulse rate, and respiration. He began to expectorate more freely, and in greater amount, he showed signs of emerging from his semi-comatose condition, he perspired freely, and began to take some interest in his surroundings. In 24 hours, the

temperature had dropped from 102.2 to 100, pulse rate from 115 to 88, with corresponding slowing in respiration from 40 to 26. The clinical picture at the end of the 48 hour period was equally progressive, temperature having fallen to 99, respiration being 32, and pulse rate 100.

Sleep was now being enjoyed for longer periods, the cyanosis was lessening, and the patient had the looks and expressed the feelings of all-round improvement. Voiding had been frequent in the meantime, although a still distended abdomen explained tardy bowel movement, which latter was satisfactorily relieved by an enema and one ampule of pituitary extract.

We maintained the potassium permanganate treatment in this case for ten days, the only deviation from the original routine being that, immediately on observing a normal chart,—in about four days after initiation of the treatment,—injections of 4 ounces of the solution every 12 hours were substituted for the 3-hourly injections. About the sixth day, there was a slight relapse, characterized by a chill, a rise in temperature, and an irregular pulse rate. The situation looked unfavorable for about twelve hours, but responded satisfactorily to medication.

Convalescence was then uneventful, and with more celerity and less fatiguing effort than is customary in a severe attack such as this was. The patient was discharged a month later, and eventually went to California to recuperate. On his return he was particular to report with the glad tidings that he felt absolutely no distressing after effects.

#### FURTHER CASES

Such was my satisfaction with the results of the first case handled in this manner, that I had no hesitation in thereafter using the potassium permanganate solution in every possible case where I considered it indicated. The following cases, treated with the standard solution at Providence Hospital, and observed personally or reported upon by others, go further to substantiate belief in this remedy in well defined pneumonia conditions.

*Case No 1812* W C Male, aged 31  
Lobar pneumonia. Very toxic when first seen—T 104.1, P 140, R 48. 5 ounces every 3 hours for 36 hours given. In 48 hours—T 98.2, P 80, R 22. 3 oz every 4 hours given for 2 days, then discontinued. Progress and convalescence uneventful. Discharged in good condition 9 days after admission.

*Case No 2013* H G Female, aged 10  
Lobar pneumonia. In great distress when first seen—T 104.4, P 126, R 24. 3 oz every 5 hours for 48 hours ordered. At end of 48 hours—T 103, P 103, R 28. Permanganate treatment discontinued at this point account of difficulty in retaining. Patient went on to a difficult recovery after having been operated on for an empyema which had developed. Left hospital in fairly good condition in about 30 days after admission.

*Case No 2337* L D Female, aged 45  
Lobar pneumonia. Given 5 oz every 3 hours for 48 hours, and thereafter continued until chart normal. Readings as follows—T 103.2, P 140, R 40. In 24 hours—T 102, P 120, R 38. In 48 hours—T 101.4, P 120, R 32. In 72 hours—T 100.3, P 109, R 30. In 96 hours—T 98.2, P 88, R 26. Recovery was uneventful. Patient was discharged in good condition after 10 days' stay in hospital.

*Case No 2634* B G Female, aged 31  
Lobar pneumonia, mitral stenosis, and preg-



nant Patient in great distress, and end seemed imminent in a few hours X-ray (portable) confirmed diagnosis in right chest Temp 103.3, P 118, R 40 Given 5 oz every 3 hours for 3 days, then reduced to twice daily In 24 hours—T 99.3, P 80, R 36 Progress continuing, discharge in good condition followed in 14 days after admission This patient delivered a 6 months fetus on second day of treatment

*Case No 901* J P Female, aged 29 Lobar pneumonia T 103.2, P 110, R 38 Given 4 oz every 3 hours for 48 hours Results at end of 24 hours—T 100, P 100 R 35 Showed great improvement at end of 48 hour period, was sleeping well, signs having abated gradually T became normal in 4 days, P staying around 80-90, with R around 25-28 Went home in ambulance after 10 days, in fairly good condition

*Case No 1839* K W Female, aged 57 Lobar pneumonia T 103, P 130, R 32 Chart readings —In 24 hours—T 102.5, P 140, R 36 In 48 hours—T 98, P 120, R 30 3 oz every 3 hours for 3 days had been given A relapse had occurred at the end of 48 hour period—T going up to 102.5, P 125, R 35 This responded to medication, chart becoming normal and so remaining Patient improved so that she was able to leave hospital by wheel chair in 13 days after admission In fairly good condition

*Case No 2069* Young child Male Lobar pneumonia Very ill and very toxic When first seen—T 106, P 148, R 45

Given 1 oz every 3 hours Retention difficult, but was persevered with and eventually controlled relapses Chart readings as follows At end of 24 hours—T 102, P 120, R 30 At end of 48 hours—T 104, P 110, R 30 At end of 3rd day—T 102, P 120, R 30 At end of 4th day—T 106, P 150, R 50 At end of 5th day—T 101, P 140, R 42 At end of 6th day—T 98, P 120, R 32 T remained normal thereafter This boy was transferred to Home in fair condition 16 days after admission

*Case No 2088* Young boy, aged 1 year Lobar pneumonia Very ill T 103.2 Was given 1 oz every 3 hours for 36 hours, reducing T one degree every day for 3 days Although several relapses intervened, T became normal in 7 days Had difficulty in retaining solution After 23 days was transferred to Home in fairly good condition

Although excellent results have been observed in private cases of pneumonia treated in the home with potassium permanganate, their details may be withheld at this time, there being a sufficiency of well authenticated institutional cases The following 14 cases were also treated at Providence Hospital, and are briefly commented upon They comprise the remainder of the original experiments with the solution, since when its exposition has been further persevered with, and with equally satisfactory results

Case History			Treatment and Progress Notes
No 2220	J C Male	Lobar Pneumonia	Given 3 oz every 3 hours for 8 days T 104, P 120, R 30 Chart showed gradual descending curve, being normal on 6th day Discharged after 14 days in good condition
Aged 30			
No 2226	P. L. Male	Lobar Pneumonia	Given 5 oz every 3 hours for 48 hours T 104, P 120, R 35 A perfectly descending curve immediately shown Normal on 5th day Discharged on 21st day in good condition
Aged 30			

<i>Case History</i>			<i>Treatment and Progress Notes</i>
No 2630 Aged 33	G C Female Lobar Pneumonia		Given 4 oz every 3 hours for 48 hours, then reduced until normal T 102, P 100, R 32 Chart is a perfect picture of a rapidly descending curve Normal in 3 days and so remained Discharged after 15 days in good condition
No 2987 Aged 23	M F Male Lobar Pneumonia		Given 5 oz every 3 hours for 48 hours T 104.5, P 130, R 50 Responded well Another perfectly descending curve Normal in 3 days Discharged after 13 days in good condition
No 3075 Aged 39	C N Male Lobar Pneumonia		Given 3 oz every 3 hours for 48 hours T 101, P 105, R 35 Good response, chart becoming normal in 36 hours, and so continued Discharged after 14 days in good condition
No 3547 Aged 36	N J Male Lobar Pneumonia		This patient made good progress under other treatment for 7 days, T having been reduced to normal, P and R in proportion Had a relapse—T 103.2, P 118, R 40 Given 4 oz every 3 hours for 48 hours Reacted well, and chart became normal in 36 hours Discharged in 19 days after entrance in good condition
No 3903 Aged 35	A G Male Lobar Pneumonia. Acute Pharyngitis Alcoholism		Patient delirious—T 101, P 120, R 30 Given 4 oz every 3 hours Did not respond T, P and R rose very rapidly Died within 48 hours in delirium tremens
No 4301 Aged 38	C T Male Lobar Pneumonia		Given 3 oz every 4 hours—T 103, P 160, R 30 In 24 hours—T 99, P 90, R 25 Maintained curve fairly even for 5 days, then had a relapse, not retaining solution well Normal curve in 2 days, and continued so Discharged after 12 days in fair condition
No 4802 Aged 32	F S Male Lobar Pneumonia		Given 4 oz every 3 hours for 48 hours T 105, P 135, R 30 T dropped 4 degrees in 24 hours Normal on 7th day and so continued Discharge in good condition in 9 days
No 4902 Aged 62	L H Female Lobar Pneumonia		T 104.2, P 100, R 30 Given 3 oz every 3 hours for 6 days Very good response, then slight relapse Continued this way for 2 or 3 days Pushed treatment Normal chart on 8th day, and so continued Discharged after 13 days in fair condition
No 5454 Aged 21	D W Male Lobar Pneumonia Pleurisy		T 104, P 120, R 40 Given 4 oz every 4 hours for 6 days In 6 hours T dropped 4 degrees, then rose for 3 days Chart normal on 5th day and so continued Discharged after 12 days in good condition

<i>Case History</i>			<i>Treatment and Progress Notes</i>
No 5506	M S Female		T 101, P 120, R 30 Given 3 oz every 3 hours. Chart curve rose slightly for 12 hours, then dropped suddenly
Aged 47	Lobar Pneumonia		—T 100, P 90, R. 28 Almost immediately patient relapsed, chart now showing a rapidly ascending curve to
			—T 106, P 130, R 40 Failed to respond, and died at end of 4 days
No 6692	J M Female		T. 103, P 120, R 45 Given 3 oz every 3 hours for 4 days Immediate response In 6 hours—T 99, P 100, R 30 Did not retain well and widely fluctuating chart until 7th day, when it became normal and so remained Discharged after 13 days in fair condition
No 8230	B J. P Female		T 104, P 150, R 56 Given 2 oz every 4 hours Immediate response In 12 hours chart read—T. 98, P 95, R 28, and so continued, except P rose again to 130, immediately falling to 70 Quick and satisfactory recovery Discharged in 4 days in very good condition
Aged 8	Bronchopneumonia		

The Providence Hospital cases above reported number 23 in all—21 recoveries and 2 deaths

#### TREATMENT UNDER ADVERSE CONDITIONS

Eloise Hospital, maintained by Wayne County Poor Commission, furnished opportunity for the exposition of the solution under a totally different set of conditions Here is the refuge of the derelicts of a community, material of possibly the worst kind

for obtaining favorable results. Twenty cases of pneumonia, all severe and all complicated, some with chronic heart conditions of long standing, and nearly all admitted chronic alcoholics, were selected at random Ten of these cases were handled by other than the potassium permanganate method, and all died. The remaining ten received the standard solution of the drug, and the undernoted tabulation represents a very fair picture of the treatment and results—fifty per cent recoveries in well-nigh hopeless circumstances

<i>Case History</i>			<i>Treatment and Progress Notes</i>
No —	W J Male		A moderately severe case T 102 2, P 110, R 40 Given 8 oz every 3 hours Did not retain well Gradual response Chart normal in 10 days Discharged in good condition after 34 days
Aged 50	Bronchopneumonia		
No —	J L Male		Given 8 oz every 3 hours T 103 2, P 130, R 55- Very good response. T dropped 3 degrees in 12 hours Chart normal in 48 hours Discharged in good condition after 23 days
Aged 45	Lobar Pneumonia		

<i>Case History</i>		<i>Treatment and Progress Notes</i>
No —	F B Male	T 104, P 100, R 30 Given 8 oz every 3 hours T
Aged 34	Lobar Pneumonia	dropped 3 degrees in 12 hours Chart normal in 48 hours Injections stopped after 4 days Discharged in good condition after 23 days
No 27449	J M Male	T 104.5, P 100, R 20 Given 8 oz every 3 hours T
Aged 49	Bronchopneumonia	dropped 4 degrees in 12 hours, then went up to 103.5 P and R continued to rise No further response Died in 2 days Pneumonia complicated with myocarditis
No 31254	T K Male	T 105.2, P 140, R 38 Given 5 oz every 3 hours In
Aged 22	Lobar Pneumonia	24 hours—T 100, P 110, R 30 Did not respond after this Chart continued to rise and fluctuate, and life prolonged for 30 days Died of pneumonia and complications
	Alcoholism	
	Narcotic Addict	
	4 plus Kahn	
No 31326	D A Male	Very ill T 102.5, P 140, R 50 Given 5 oz every 3
Aged 42	Lobar Pneumonia	hours Did not retain well, and response was poor Became normal for 12 hours after 7th day Had relapse, went into delirium, and died on 12th day—pneumonia and myocarditis
No 31823	J K Male	Was very low on entrance Given 7 oz every 3 hours
Aged 35	Lobar Pneumonia	Did not respond Became very toxic and died within 24 hours—pneumonia and myocarditis
	Empyema	
No 32595	J S Male	Was in straight jacket during treatment T rose to 106,
Aged 28	Lobar Pneumonia	P 140, R 50 Died in 10 days—pneumonia and alcoholism
	Delirium Tremens from Alcohol	
No 32693	F K Male	Was in delirium on admission T 103, P 120, R 45
Aged 45	Lobar Pneumonia	Given 5 oz every 3 hours Responded well, Gradual improvement in chart, normal in 6 days and so remained Discharged in 17 days in good condition
No —	J S Male	T 104, P 120, R 30 Given 8 oz every 3 hours Did
Aged 32	Lobar Pneumonia	not retain well at first Pushed solution In 12 hours—T 100, P 90, R 25 Chart fluctuated widely for 4 days, becoming normal on 7th day, and so remaining Recovery uneventful

In order to arrive at a true appraisal of the value of the potassium permanganate treatment in the Eloise cases, it must be remembered that the patients were of the most indigent and homeless type Excesses, undernourishment, and in most cases, long exposure to the elements, had reduced

vitality and resistance to infection to a very low point Gathered from the streets of the city, as public charges, they had come here to die One hundred per cent mortality had been the rule under similar conditions and orthodox treatment in the past We are confident that where death was

delayed, it was altogether because of the potassium permanganate. Where it happened quickly, the solution had come too late for any possible results. The recoveries were prompt, and in the nature of a surprise to the staff of the hospital.

#### POSSIBILITIES IN OTHER DISEASES

Although my more intimate acquaintance with the solution has been practically confined to acute cases of pneumonia, I was at once struck with the possibilities of its extension to other diseases. I find that these are more than favorable, inasmuch as a great variety of conditions have been treated by this method and reported upon. Dr. Nott notes receipt of information from interested correspondents that it has proved beneficial in the following instances — pneumococcal meningitis, cerebro-spinal meningitis, acute bacillus coli infection, acute rheumatoid arthritis, cardiac asthma and dropsy, angina pectoris, eclampsia, gout, diabetes, gastric ulcer, colitis, chorea, certain skin infections, and other composite cases. Indications were to the effect, however, that mixed infections were somewhat less responsive, and in most cases the termination was by lysis instead of crisis.

#### EFFECTS ON BLOOD PRESSURE

In the course of the preliminary experimental work and during the early practice of this therapy in England, it began to be noticed that some detoxicating process was taking place in the blood as well as in the tissues, in cases recognized as of toxic origin. Con-

firmatory evidence began to accumulate that the solution had its influence on the blood pressure, and was often successful in lowering high tension. Dr. Nott has reported (*The British Medical Journal*, December 26, 1925) on a long list of such cases in the belief that, whatever they proved, they at least justified the recording of certain impressions which it was hoped would be found sufficiently interesting to stimulate further inquiry.

#### CHEMICAL ACTION

There are three stages in the reduction of potassium permanganate corresponding with the separation of 1, 3, and 5 atoms of oxygen per two molecules of salt. The decomposition products are, respectively, potassium manganate, manganese dioxide, and manganous salt. Two gram-molecules of potassium permanganate contain the equivalent of 80 grams of available oxygen, which is rapidly given off in the presence of water. The residuum, being manganese dioxide, is an antiseptic and an antidote for certain poisons. It is asserted to be the most efficient antidote to snake venom. What then are its effects on the toxins produced by pneumonia? Dr. Nott, again, is impressive in his attempt to forestall this anticipatory question. He says:

"Let it be remembered that the human toxins have long been known to resemble snake venoms, that snake venoms are of metabolic origin, and, numerous as they are in number, variety and potency, potassium permanganate is an antidote to all, or nearly all. A significant fact is that all venoms act on the animal body in one of two ways, and can be grouped under two physiological

headings They are either hemotoxic or neurotoxic in their action, death occurring from changes in the blood or from paralysis Now, if the human body is producing toxins resembling snake venom, is it not possible that we poison ourselves by our venoms affecting the blood and the nervous system? And if potassium permanganate in minute quantities is an antidote to snake venoms, why not also to the human venoms?"

### A SIMPLE THERAPY

The potassium permanganate treatment is inexpensive, easily understood, and admirably adapted for ordinary home nursing Its very simplicity tends to detract attention from its potency and efficiency in certain grave toxic and infectious conditions, and this fact alone may have had something to do with its being so long overlooked by the profession as a remedy promising favorable results in pneumonia One does unconsciously look for intricate technic in the employment of new remedies In my experience with it, I have had occasion to comment on inattention and even reluctance on the part of some nurses caring for private cases in homes, during a course of treatment I invariably attributed this to the fact that they were being called upon to handle as the chief weapon, something they had been accustomed to consider as a by-product, a minor aid and appurtenance to some other major remedy

Simple and non-technical as the treatment is, yet, it has its inhibitions The tablets or crystals should have no place on the shelves of the family medicine cabinet with the commoner domestic remedies, which can be and are used promiscuously for minor ailments

They should only be used under the physician's directions, and they must be pure The tablets, which are freely soluble in water, are probably more reliable than the commercial crystals, and are therefore to be preferred in the preparation of the solution

Injection by means of a funnel and catheter is given, with the patient lying on his left side, and must be made carefully and slowly, otherwise a spasm of the bowel will result, and entrance be denied The ideal time for the injection is about half an hour after a bowel movement, when a cleansing enema might well be given, retention being more satisfactory when the solution is comfortably hot The quantity and strength of the solution, and the length of time between injections, will vary according to the individual needs and circumstances of given cases The factors of age, severity of attack, and capacity of retention, in turn will govern the procedure Mucous casts of the bowels may be encountered during the progress of the treatment, and should be warned against and discounted

Dr Nott mentions the cachet method of administration— $\frac{1}{8}$  to  $\frac{1}{2}$  grain of the powdered drug enclosed in a small sized cachet, and swallowed with half a point of hot water In cases where rectal injection is not practicable, I presume that this method would have its advantages, and I would welcome a verdict from interested observers on the subject I see no reason why the solution could not, under proper instructions, be self-administered rectally in ambulatory cases, but

I would sound a note of warning against irresponsible and uninstructed treatment

There is too great a possibility of inducing poisonous symptoms, to encourage the adoption of a "home remedy" attitude towards the treatment, and to allow the prescription to be handed around indiscriminately. By all means let the first injection be made under the personal supervision of a physician or capable nurse, and see to diminishing color, the disappearance of it that the others are made according to scientific directions. Then will this treatment be reassuring to the patient, then will the home properly join with the institution in furnishing the indisputable proofs as to whether principle or theory is to govern the decision — is potassium permanganate a specific in pneumonia?

#### IS IT A SPECIFIC?

Witness the lung signs, cyanosis invariably present and oftentimes extreme, the high temperature, the quickening of respiration and pulse rate, the harsh, strained bark of a labored cough, and the rusty red sputum difficult of expectoration. Observe the restlessness, the fitful sleep, the lassitude that presages lack of interest in life or death, slowly developing into delirium, stupor, and sometimes complete unconsciousness. Pneumonia in its many manifestations!

Conceive the clinical picture being rapidly changed by this new therapy to an awakened interest in surroundings; a lowering in temperature and pulse rate, slower and deeper respira-

tions,—all in a matter of a few hours. Observe, as I have done in many instances, the cyanosis disappearing, the rusty sputum coming up freely and in restlessness and sleeplessness, — in twenty-four hours. I have noted temperature, pulse rate and respiration become normal in from forty-eight to seventy-two hours after the first injection, and I have seen patients pronounced in good condition and fit to be discharged in a shorter time than I would have believed possible under any other regime.

The suggestion would be that potassium permanganate has all the earmarks of having a true specific action on the micro-organisms of pneumonia. Apart from the English cases I cannot find that a determined effort has been made to really test its efficiency. The very prevalence of an infection so virulent and intractable as this is should be sufficient to encourage widespread efforts to discover whether or not the hopes already engendered for the treatment are founded on good and sufficient premises.

The beforementioned experiments and treatments were made possible by hearty co-operation and assistance on the part of the following — Doctors C. T. McClintic, J. Agins, E. J. Panzner, F. S. Porretta, E. C. Texter, C. P. Sibley, A. O. Brown, B. H. Priborsky, W. J. Seymour, E. H. Carroll, H. L. Perlis, L. J. Cariepy, H. F. Raynor, L. J. Bailey, J. M. Burgess, A. K. Northrop, J. N. Jaekel, Geo. A. Trizisky, Chas. A. Lilly, J. E. Bennett, D. U. Saunders, A. J. Hollander, H. Charney, W. Koester, F. F. Cameron.

# Total Base In Gastric Contents And Gastric Secretion\*†

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**S**TUDIES of the gastric juice have centered largely around the question of acidity and little attention has been paid to the base in the gastric secretion. Since Reaumur isolated the gastric juice and proved its solvent action on ingested food, gastric secretion has been the subject of extensive research. But Young's observation that the secretion is strongly acid, and Prout's that the acid is hydrochloric directed study to the acids with almost total indifference to the other constituents. It is only comparatively recently that anything has been done with regard to the determination of total chlorides. Inasmuch as the bases are concerned vitally in the secretion of acid and in its neutralization, they are in many respects as deserving of study as the hydrochloric acid.

There have been numerous hypotheses as to the mechanism of the production of hydrochloric acid in the stomach. Maly advanced the idea that it resulted from the interaction of two salts of sodium, sodium di-hydrogen phosphate and sodium chloride,  $\text{NaH}_2\text{PO}_4 + \text{NaCl} \rightarrow \text{HCl} + \text{Na}_2\text{HPO}_4$ \*\* He believed the reaction to be intracellular. Harvey and Bensley, and

others, expressed the belief that the reaction which results in the formation of hydrochloric acid takes place in the foveola of the gland rather than in the cell. Collip, in 1912, by microchemic methods of precipitating phosphates, chlorides, and carbonates in the tissues of the gastric mucosa, demonstrated a definite change in the chemistry of the parietal cells and the intracellular tissue during rest and activity. During rest, chloride was present in abundance in the interstitial tissues, and phosphate and carbonate predominated in the parietal cells. During activity, the presence of all three radicals was demonstrated in the parietal cells. Since little potassium could be found, he assumed that most of the cation present was sodium.

Concerning the bases and their rôle

\*The work was done under the supervision of Dr Leonard G Rowntree and is one of three studies. One of the two studies which will be published later is on the quantitative determination of gastric secretion by Dr H V Dobson, and the other on the quantitative study of the different bases in the gastric juice by Dr Theodore Bliss.

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\*\*This reaction does not occur in vitro.



there is little accurate information Boldyreff, in 1915, postulated the theory that the bases in the gastric juice were derived from regurgitation of alkaline fluids (bile, and pancreatic and intestinal juice) from the intestine, and that this was responsible for the automatic regulation of gastric acidity Bell and MacAdam, Appelly and others have supported this theory

### METHOD OF STUDY

The present study was undertaken with the idea of determining (1) the total base present in gastric secretion, (2) whether it is secreted as such by the gastric mucosa, and (3) the variations in total base during fasting, during the secretory phase, and in various pathologic states

During the course of my work an article appeared by Gamble and McIvar on the fixed base in the gastric juice. However, they used a test-meal as a stimulus and reported a wide range of base in gastric secretion, whereas I used histamine. The patients under observation were from the gastro-enterologic service, and a dog, weighing 12 kg, with a Pavlov pouch was used as a control. Observations were also made on seven normal persons.

The reaction to histamine, administered subcutaneously, is preferable to the test-meal in the study of gastric secretion because extraneous material is not introduced into the stomach and, in calculating results, correction for dilution is not necessary. In the first twenty cases a dose of 0.25 mg was used, but later 0.1 mg was found to be sufficient to stimulate secretion and

proved to be more satisfactory. This amount of histamine was found efficacious in the stimulation of secretion in some cases in which there was achlorhydria with the test-meal. The smaller dose is preferable because it results in a shorter secretory phase and permits the determination of change in secretion both at the beginning and at the end of the secretory phase. The smaller dose is also advantageous because it may be used without the disagreeable physiologic effects, such as reversed peristalsis with reflux of duodenal contents, and lowered blood pressure accompanied by headache and uncomfortable flushing, which are sometimes encountered when a larger amount of histamine is administered.

On the morning of the examination the subject to be tested was not given breakfast, and the contents of the stomach were aspirated and saved. Histamine was administered and subsequently aspirations were made every fifteen minutes. In the earlier tests, when the larger doses (0.25 mg) of histamine were used, the specimens were taken at intervals of fifteen minutes, placed in one container, and a single analysis made. With the administration of smaller doses of histamine and the resultant shorter secretory phase, each aspirated specimen was examined separately. Total acid, free acid, chloride and total base in each specimen were determined. The presence of bile or mucus was noted and graded.

The dog that was used in the experiments was continuously in a healthy condition and served, I believe, as a normal control. Secretion from a Pavlov

pouch is pure gastric juice uncontaminated by saliva or duodenal contents. Because of the small size of the pouch it was necessary to prolong the secretory phase in order to obtain sufficient secretion for analysis. Doses of histamine of 0.1 to 0.5 mg were used and the contents of the pouch were collected at intervals of an hour. Toward the end of the series of experiments, the opening of the pouch became smaller, and it was therefore possible to collect secretion in the morning before food was given comparable to the contents of the stomach collected in the morning from the patients studied.

The usual method of titration with 0.1 N sodium hydroxide was used for total and free acidity, phenolphthalein being an indicator for the former and dimethyl-amino-azobenzol for the latter. The determination of chlorides was carried out by the Volhard-Harvey method. The total base was determined by the method of Stadie and Ross, the only departure from the original procedure being in the removal of phosphates. According to their technic, phosphates are precipitated by the addition of an equivalent amount of 0.1 N ferric alum. This requires separate determination of phosphates. In working with the gastric juice, this is impractical because the occasional presence of bile interferes with the use of direct colorimetric methods of estimation, and the "wet ash" method is laborious and tedious. Gastric juice contains only small amounts of phosphate, so the process was simplified by the addition of 0.2 cc of 0.1 N ferric alum to

precipitate the phosphate and the excess iron was removed by means of 4 N ammonium hydroxide. Acidity is expressed in the conventional way and base likewise as cubic centimeters of 0.1 N acid or base for each 100 cc of contents.

#### FASTING SECRETION FROM SEVEN NORMAL PERSONS

The contents of the stomach taken after fasting from seven normal persons (laboratory workers) were aspirated and examined for free hydrochloric acid, total base and bile. This was done in order to establish a normal for the content of the human stomach after fasting. Hydrochloric acid was present in only two instances in which it was 10 and 29 and the total base 92 and 90, respectively. In the other five subjects the total base was 101, 102, 102, 108 and 126, respectively. Objection has been raised to using the contents of the stomach after fasting because of the claim that it is largely swallowed saliva. In this connection it was interesting to find that the saliva of these persons averaged 52 cc while the average base for the contents of the fasting stomach group as a whole was 102 cc 0.1 N base for each 100 cc.

#### GASTRIC SECRETION AFTER STIMULATION WITH HISTAMINE

*Nine cases of normal hydrochloric acid content*—In this group total acids varied from 35 to 56 cc of 0.1 N acid for each 100 cc and free acid from 10 to 40 cc. The total base at the height of the secretory phase ranged from 82 to 86 cc 0.1 N except in one in-

TABLE I  
RESULTS OF ADMINISTRATION OF HISTAMINE IN SELECTED CASES

Case	Fasting				Fifteen minutes				Thirty minutes				Forty-five minutes				One hour				One hour and fifteen minutes				Comment
	Total acid	Free acid	Total base	Chloride	Total acid	Free acid	Total base	Chloride	Total acid	Free acid	Total base	Chloride	Total acid	Free acid	Total base	Chloride	Total acid	Free acid	Total base	Chloride	Total acid	Total base	Chloride	Histamine, mg	
1	40	22	82	78	56	40	68*	72	56	40	68*	72	56	40	68*	72								0.25	Normal acids, neurosis
2**	6		128		6		92		26	16	82		50	30										0.1	Normal acids, arthritis
3***	56	30	84		104	90	28		92	88	34		84	78	98									0.1	Hyperacidity, gastric ulcer
4	16		90.5		64	52	60.4		90	74	50.6		66	53	60.4		70	52						0.1	Hyperacidity, arthritis
5	4		102	82	6		92*	78	6		92*	78	6				8		144**	72	18	144		0.25	Achlorhydria
6	10		76		8		86		8		86		8				10		106***		10	106**		0.25	Achlorhydria
7	32	20	156	74	66	54	112	102	44	54	112	102	24	28	120	88								0.1	Gastroenterostomy
8	20	8	116	84	62	48	104	96	56	42	120		52	30	136	88								0.1	Gastroenterostomy

\*Fifteen, thirty and forty-five minute==specimens pooled

\*\*One hour and one hour and fifteen minute==specimens pooled

\*\*\*Bile was not present

stance In this case the base at the height of secretion was only 68 cc and curiously enough was in the patient with the highest acidity (56 total, 40 free)

The inverse relationship of acid and base is shown in Table I In Case 1 the free acid increased from 22 to 40 and the base decreased from 82 to 68 In Case 2 the free acid increased from 0 to 30 and the total base decreased from 128 to 82

*Six cases of hyperacidity*—In this group the total acids varied from 62 to 120 cc of 0.1 N acid and the free acid varied from 47 to 102 cc The total base varied from 28 to 85 cc 0.1 N for each 100 cc of contents Two instances showing the inverse relationship are given (Cases 3 and 4, Table I) Case 3 is one of gastric ulcer in which the free acid increased under stimulation by histamine from 30 cc of 0.1 N to 90, returning to 78, and the base decreased from 84 to 28 cc, returning to 98 cc at the end of the period of forty-five minutes

*Seven cases of benign achlorhydria*—The concentration of total base in patients with benign achlorhydria was found to be higher than in normal persons or patients with hyperacidity Administration of histamine was not followed by the appearance of hydrochloric acid in four of the six cases studied It is extremely significant, however, that in these four cases increased secretion of total base resulted The increase in concentration of total base, with failure to liberate hydrochloric acid, calls for further investigation The effect of stimulation by

histamine is given for Cases 5 and 6 (Table I) In Case 5 the base after fasting was 102 cc 0.1 N At the end of an hour the base was 144 cc and free hydrochloric acid was not secreted In Case 6 the base increased from 76 to 86 cc at the end of fifteen minutes and to 106 cc at the end of an hour and fifteen minutes A trace of bile was present in each of these specimens, indicating regurgitation of duodenal contents

*Nine cases of gastro-enterostomy*—The concentration of base in this group was the highest found in any of the series Free hydrochloric acid was present in all but one case, despite the fact that bile was present in every specimen The inverse relationship of concentrations of acid and base is shown in Cases 7 and 8 (Table I) In Case 7, the free acid increased from 20 to 54 cc of 0.1 N acid and the base decreased from 156 to 112 cc 0.1 N and later rose to 120 In Case 8, the free acid increased from 8 to 48 cc and the base decreased from 116 to 104 and later rose to 136

*Results in the dog (eight experiments)*—In the juice of the dog after fasting the free acids varied from 0 to 12 cc of 0.1 N for each 100 cc The total acid was likewise low, varying from 10 to 16 cc of 0.1 N acid On the other hand, the bases were very high, ranging from 115 to 150 cc N Following the administration of histamine, as the secretion of acid increased, invariably the concentration of the base decreased, while later with the decline of the secretory phase the free

acid decreased and the base increased in concentration and approached its former level (Fig 1). The most striking results are seen in Experiments 1, 2 and 3 (Table 2). In these experiments, the total acid reached 120, 140 and 108 cc of 0.1 N for each 100 cc, respectively, two hours after

the administration of histamine. The free acid reached 80, 130, and 92 cc, while the base, which was well above 100 in the contents on fasting in each instance, had decreased to 23, 74 and 60 respectively. The similarity of response in the dog and in patients is shown in Figure 2.

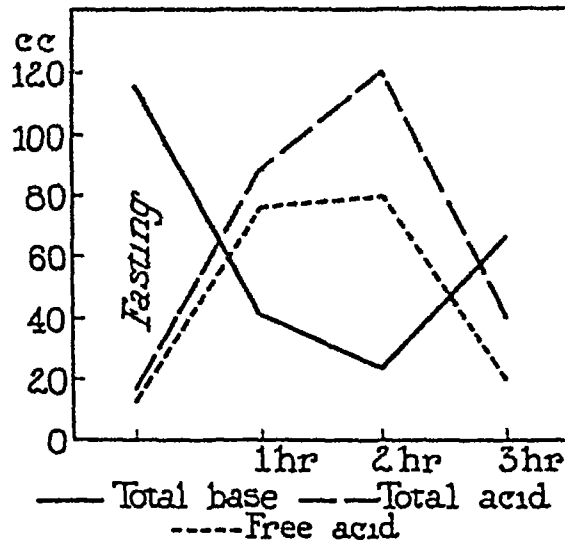


FIG 1 Secretion from dog. Reciprocal relationship of acid and base during the entire secretory phase. (The ordinate represents cubic centimeters of 0.1 N acid and base for each 100 cc of solution.)

TABLE 2  
GASTRIC SECRETION OF THE DOG

	Experiment 1			Experiment 2			Experiment 3		
	Total acid*	Free acid*	Base, total**	Total acid*	Free acid*	Base, total**	Total acid*	Free acid*	Base, total**
Fasting	16	12	115	10		134			150
First hour	88	76	42	110	90	33	98	68	68
Second hour	120	80	23	140	130	74	108	92	60
Third hour	40	20	65		Amount not sufficient		100	80	65

\*Acid expressed as 0.1 N acid for each 100 cc of solution

\*\*Base expressed as 0.1 N base for each cc of solution

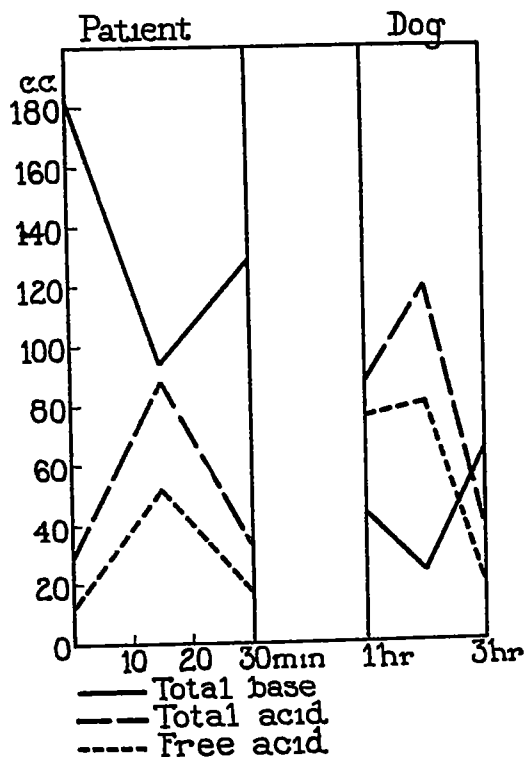


FIG 2 Data charted together to show the similarity of reaction during the secretory phase (The ordinate represents cubic centimeters of 0.1 N acid and base for each 100 cc of solution)

*Variation in the curve of the chloride*—The curve of the total chloride during the secretory phase varied with the curve of the acid. The total chloride tended to increase in concentration during the secretory phase. The bound or base chloride was calculated by subtracting the total acid from the chloride (8). The base chloride was higher in the contents of the stomach on fasting than at the height of the secretory phase. It would seem that during secretion the base chloride has been largely converted into hydrochloric acid. The base chloride in hyperchlorhydria was found to be extremely small in amount, whereas in hypochlorhydria it was present in large amounts (Fig 3).

*Phosphate content of the gastric secretion*—Quantitative estimations of the phosphate in the gastric secretion were made in a few cases and also in the secretion from the dog. The phosphates did not show significant variation during the secretory phase.

#### COMMENT

The most significant observations in relation to the total base in the various groups of cases are shown in Table 3. From this it will be seen that the lowest concentration of total base in the gastric juice is found in patients with hyperacidity, and the highest in patients with achlorhydria, and particularly in patients who have been sub-

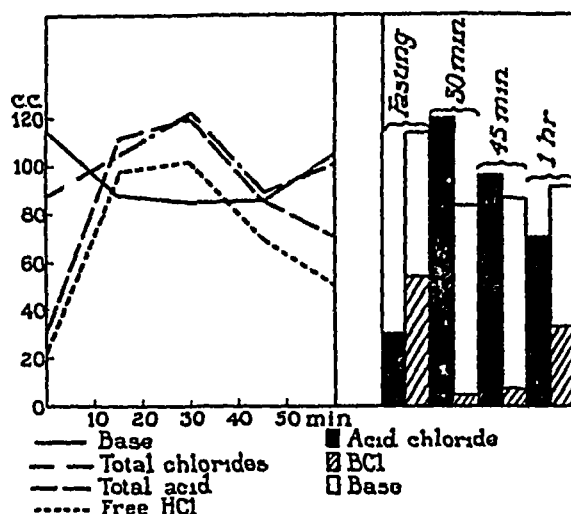


FIG 3 Typical relationship of acid and base The chloride curve follows directionally that of the acid but this base chloride diminishes during secretion

TABLE 3

THE AVERAGE TOTAL BASE DURING THE FASTING STAGE AND SECRETORY PHASE FOR ALL CASES

	Cases	Fasting, cc 0.1 N for each 100 cc	At height of secretion, cc 0.1 N for each 100 cc
Normal hydrochloric acid 10-40	9	91.2	63
Hyperacidity, free hydrochloric acid above 40	6	105.8	81.8
Benign achlorhydria	7	113.3	90
Gastro-enterostomy with free hydrochloric acid	8	134	97
Gastro-enterostomy without free hydrochloric acid	1	142	142

jected to gastro-enterostomy. This is true for secretion during fasting and for the secretion after stimulation by histamine. The curve for secretion of the total base following the use of histamine is in inverse relationship with the curve of the total and free acid. This is true for normal persons and the normal dog, and is also evident in the various pathologic conditions studied. As a rule, stimulation by histamine results in increased secretion of acid and diminution in the secretion of the total base. In benign achlorhydria

in several instances, however, histamine has resulted in increased secretion of base.

Gastric juice normally contains considerable amounts of base. During the secretory phase, the total base varies simultaneously with the secretion of acid, but in the opposite direction, thus exhibiting an inverse relationship. Gastric secretion involves changes in the concentration of both acid and base. The study of the bases in gastric secretion is as worthy of consideration as is that of the acids.

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# Postinfluenzal Vomiting With Symptoms Of Lethargic Encephalitis

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**D**URING the past few months, in a practice consisting chiefly of diseases with prominent symptoms referable to the alimentary tract, there have come to attention several unusual cases in which the chief complaint was vomiting; and examinations failed to yield data upon which they could be classified in any of the well-known groups of conditions in which vomiting is an outstanding symptom. A cursory investigation among other members of the medical profession of this city brought to light a few similar cases, diagnosed doubtfully as "neurotic vomiting," "nervous indigestion," or "food poisoning." In each instance, the physician could not recollect with certainty having encountered such cases during the six preceding years.

In all of these cases there were some of the symptoms found in epidemic encephalitis, and in none were there symptoms incompatible with that diagnosis. In view of the present wide-spread epidemic which bears so many features in common with the epidemic of "influenza" of 1918, and the fact that neurologists are again finding cases of *advanced* lethargic encephalitis of the influenzal type, it seems probable that the cases herewith

reported represent a condition of *mild epidemic (lethargic) encephalitis* (sleeping sickness).

A report of this nature is made at this time because in spite of the voluminous literature on epidemic encephalitis, little note is taken of early cases except from a neurological point of view, and the striking symptoms mentioned below suggest instead disease of the gastro-intestinal tract.

Von Economo, in the first paper to attract much attention, his original article (1) written under the stress

(1) Economo, C. von. *Encephalitis lethargica*, Wien Klin Wochschr 30, No 19 581, May 10, 1917.

of war times, described only advanced or outstanding examples of this disease. But Hall (2) described a case

(2) Hall, Arthur J. *Epidemic Encephalitis*, Wm Wood and Co., 1924, P 5.

among his records of 1903 with cardinal symptoms of malaise, somnolence, incoordination of eye movements, nausea, vomiting and fever, of one week's duration. This patient gradually improved and went on to complete recovery except for twitching of the face that persisted even after several years.

The three commonest symptoms of epidemic encephalitis are malaise, lethargy and ophthalmoplegia. In *acute* epidemic encephalitis that has advanced to the stage of obvious seriousness, the mortality is as high as 40 per cent, yet many of these cases do apparently make good recoveries. As the years pass, however, it is being recognized that *residua*, often inconspicuously slight, remain in a large proportion of these individuals. The *chronic* cases that have advanced to the stage of paralysis agitans of course are more apt to remain badly affected.

The cases herewith reported are believed to be examples of *mild acute epidemic encephalitis*.

*Case 1*—An active chemico-mechanical engineer, twenty-five years old, had enjoyed good health, worked hard, and slept about seven hours each night for many years. The members of his family all had "flu" in the fall, but he was the least affected and never lost a day of work. However, from that time on, he felt tired and finally suffered with *malaise* so extreme that the least effort made him feel "all in." He had to force himself to get up in the morning. He had no energy to carry on his work at the office, and by noon his legs felt so "wobbly" that he had to go home and rest.

*The thing that brought him to the doctor was nausea and vomiting.* He felt nauseated continuously and vomited as often as six times a day. This had gone on for a week. He described his sensation as that of being seasick. He thought he had "nervous indigestion," and a pathologist had told him that he was vomiting because his wife was pregnant.

The vomiting had started rather suddenly, and he vomited before breakfast but never brought up food eaten the evening before. He seldom brought up more than a third of a cupful of colorless, slightly bitter fluid.

He absolutely denied pain of any kind and had no headache. He passed formed stools daily without using cathartics. He said he would have been hungry were it not for the nausea, yet he ate his meals and had lost only five pounds during the four weeks of his illness.

He was dizzy most of the time, but did not display any tendency to fall to one side or the other. He admitted that his dizziness was quite troublesome and was apparently a part of the "seasickness" of which he complained.

When questioned in regard to his habits, he gave a surprising story of recent *somnolence*. Since his present illness began, he *felt sleepy all of the time—would sleep* soundly twelve hours at night, take a long nap in the afternoon, and in the evening while a noisy party was going on at his house he would lie down on the davenport and sleep soundly "for two and a half hours, until the dishes were all washed and the guests were going home."

He denied double vision.

He denied numbness, unilateral weakness, symptoms referable to the special senses and to the central nervous system except as mentioned above.

He denied symptoms referable to the nose and throat, the trachea and lungs, the circulatory system, the urinary and genital system, and the joints. He denied "hives" and other symptoms referable to the skin.

He smoked twenty cigarettes a day, and had been doing this for several years, but his symptoms persisted after he had stopped smoking for a week.

Three months earlier, he had been worried about one of his employees, but the difficulty was settled, and he denied worrying about anything since his recent illness began.

He denied being near the fumes of poisonous chemicals.

He had never suffered any similar previous illness.

Examination failed to reveal any focus of infection of the upper respiratory tract. The tonsils had been removed. The sinuses seemed to be in good condition, and X-ray plates failed to reveal dental caries.

There was slight drooping of the eyelids but no evidence of muscle palsy, no irregularity of the pupils, and no noteworthy alteration in the eyegrounds. Tests failed to detect labyrinth disorder, and reflexes from the turning test were slightly less than the average time.

Except for appearing weary, the patient's features were not changed and his skin was not oily. His blood pressure was 105/60, his pulse rate 70, and his *temperature 99 degrees*.

Nothing noteworthy was found upon examination of the chest. The abdomen was flaccid and peristaltic sounds were normal. The kidneys were not palpable.

Abdominal reflexes were brisk and equal. The knee-jerks were weak, even when supplemented, but equal, so also were the triceps jerks. Babinski's sign was absent. Careful tests for sensory disturbances failed to show any departure from the normal.

Laboratory tests on the blood, urine and stool were essentially "negative" except for an *increased white cell count*. This varied between 10,000 and 12,300 when examined on several occasions, and the polymorphonuclear neutrophils made up approximately 75 per cent of this number. No parasites were found in warm fresh stools.

This patient presented symptoms characteristic of a low-grade toxemia, with vomiting of cerebral origin. The differential diagnosis included poisoning from chemicals at the shop, poisoning from excessive use of tobacco, focal infection of the upper respiratory passages, lungs or gallbladder, and cerebral disturbances on a basis of worry or nervous exhaustion. None of these were satisfactory. The diagnosis finally made was low-grade encephalitis, and the subsequent course of the case seemed to substantiate this impression.

Over a period of months, he slowly but steadily improved. The vomiting stopped after ten days, but the malaise, vertigo and somnolence continued. After five weeks, the vertigo was gone. After seven weeks, the somnolence had changed to insomnia. Ten weeks later he was again drowsy. After five weeks he felt good except for the malaise. He had gained five pounds,

had a temperature under 98.8 degrees and a leucocyte count of 8,000. But during the tenth week he developed a right-sided headache, and the *right pupil became larger than the left*. He said he again found an occasional temperature of 99.5 degrees, but no fever was noted upon occasional trips to the office.

*Case 2*—A man forty-five years old had the "flu", but was the least affected of any member of his family. He grew more and more tired thereafter, found he could not read as well as formerly, and awoke one morning dizzy, *nauseated and vomiting*. He became unusually drowsy. His bowels remained regular without the use of cathartics. He called the doctor because he thought he had "indigestion". He had a slow pulse, no fever except on one occasion and then it was slight, a slightly increased white cell count, sluggish reflexes and very poor ocular convergence. His course paralleled that of the preceding one.

*Case 3*—A nursemaid, single, thirty-five years old, had a mild attack of "flu". A week later, she felt *nauseated and vomited*. Her menses were regular. She had no fever. She had no bowel disturbances. She had a slight headache. She had no eye symptoms or findings. She was sleepy and tired. The vomiting stopped after three days, and except for malaise and somnolence, she has been all right since.

*Case 4*—A lunch-room owner awoke one morning with *nausea, vomiting* and diarrhoea. He had a slight fever and leucocytosis. His wife who had eaten the same kind of food as he at both the noon and evening meals of the preceding day was well. After a week, the vomiting and diarrhoea gradually disappeared, but he remained drowsy and tired for sometime thereafter.

*Case 5*—A married woman 35 years old with negative Wassermann and Kahn tests had had several induced miscarriages. Menses were painless and regular and vaginal examination revealed no tenderness nor masses. She denied having had the "flu" but the other members of her household had it "bad". She began to have trouble.

keeping type in focus when reading, and a month later went to see the doctor because of *nausea, vomiting* and malaise. She had a slight fever and slight leucocytosis. She also improved gradually.

As may be noted in the above cases, superficially there is much resemblance to a host of ordinary conditions such as tabes, pregnancy, food poisoning, or salpingitis. The following symptoms seem to be more or less characteristic of this disease, although they are seldom all found in the same patient:

Vomiting without necessarily abdominal pain or diarrhoea,  
nausea, continuous or remittent,  
vertigo,  
somnolence, often followed by insomnia,  
marked malaise,  
eye disturbances or symptoms referable to the labyrinth,  
fever, very slight and intermittent,  
leukocyte count slightly elevated,  
course of several weeks to several months.

Spinal punctures were not done because even in advanced cases of lethargic encephalitis there are seldom marked changes in the fluid pressure, globulin or cell count.

Of course there is no absolute proof

of the specificity of such cases, even though they go on into the advanced stages of paralysis agitans<sup>1</sup>. For that matter, the causative organism of "influenza" has never been positively identified, nor its relation to the epidemic encephalitis of 1918 indisputably established.

There are individuals who suffered with extreme malaise, vertigo, somnolence and vomiting after they had a mild attack of "flu" in 1918, and who state that they have never felt that they completely recovered. Some of them still have slight visual disturbances and other chronic ailments on a nervous basis.

Attention is directed to these cases in the hope that more specific diagnoses can be made and that the situation will become clarified through wide-spread recognition and study.

#### CONCLUSIONS

Unusual cases of vomiting have appeared during the recent epidemic of "influenza."

These seem to bear a close relation to lethargic encephalitis.

Vestigial disturbances remain in many individuals similarly affected during the pandemic of 1918.

# Summary of Investigations on the Etiology of Tropical Sprue in Porto Rico\*†

By CHARLES WEISS, Ph D, M D, FRANCISCO LANDRON, B Sc, OSCAR COSTA-MANDRY, M D, D M, AND DOROTHY WILKES-WEISS, M D.

THERE has been noted in recent years a growing interest in the study of so-called "tropical sprue" This is due largely to the increasing number of cases recognized in sub-tropical and temperate regions For example, Thaysen reports five cases of sprue originating in Denmark, Lambright describes a case from Cleveland, and the observations of Wood in North Carolina and Silverman in Louisiana show that the disease is not at all uncommon in those states

A second stimulus has been the suggestion promulgated by Wood, Christian and others, and supported by recent studies on liver therapy in certain types of anemia, that sprue and pernicious anemia are not only closely related disorders but may be phases or stages of the same disease

It has therefore seemed to the writers that the following summary of studies on sprue in Porto Rico, where as Ashford has frequently

pointed out, the disease is prevalent, might be of general interest

## *I—Epidemiology*

According to the records of the Bureau of Vital Statistics of the Department of Health of Porto Rico there were 322 deaths from sprue during the period July 1, 1924 to December 31, 1927 A large majority of these deaths were distributed among the populous municipal districts, or counties, along the coast, that of Ponce (population 76,200) heading the list with 85 deaths, San Juan, the capital, (91,600), second, with 36 deaths, and Mayaguez (43,000), third, with 27 deaths

The relatively small number of sprue deaths reported from the high hilly interior, where there is a dense rural population and some ten towns of three to fifteen thousand population at altitudes of 400-2200 feet, may be due to climatic factors, such as lower mean temperature with greater diurnal variations, heavier rainfall, less sunshine, etc, but can be explained by conditions of medical practice A much larger percentage of the sick in the interior are not attended by physicians, so that diseases like sprue, in which the diagnosis depends on careful examination, are likely to pass unrec-

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†Presented before the American Society of Tropical Medicine at Washington, D C, May 1, 1928

ognized Even in the larger coastal cities where doctors are in reach of everyone, it is well known that certain physicians see many cases of sprue while others report few, the difference being due not so much to variations in clientele as to lack of agreement as respects criteria of diagnosis (Table I)

Under 5 years	5 cases
5- 9 years	3 cases
10-19 years	1 case
20-29 years	11 cases
30-39 years	16 cases
40-49 years	20 cases
50-59 years	23 cases
60 and over	6 cases

It is noteworthy that most of the

TABLE I

DISTRIBUTION OF DEATHS FROM SPRUE IN THREE GROUPS OF MUNICIPALITIES OF PORTO RICO

Group No	Groups of Selected Municipalities	Total Population	Total No of deaths 2½ yrs
1	Northern Coastal Municipalities*	239,500	82
2	Central Mountainous Municipalities	1,420,000	322
3	Southern Coastal Municipalities Entire Island of PORTO RICO	231,200 231,850	155 32

\*Group 1 includes Aguadilla, Hatillo, Arecibo, San Juan, Rio Piedras, Rio Grande and Fajardo

Group 2 includes Coamo, Ciales, Aguas Buenas, San Sebastian Morovis, Cayey, Aibonito, Caguas, San Lorenzo, Juncos and Humacao

Group 3 includes Mayaguez, Cabo Rojo, Ponce, Guanica, Salinas, Guayanilla, Yabucoa, Guayama, and Santa Isabel

In respect to racial incidence, we note that among the recorded deaths from sprue, there were 261 white, and 61 colored, or a ratio of more than 4 to 1, while the proportion of whites to colored in the general population is officially stated to be about 3 to 1

There is a slight excess of females over males in the series, the figures being 170 and 152 respectively

From the records of the Presbyterian Hospital of San Juan (70 beds), where 85 sprue cases were treated from July 1, 1924 to December 31, 1927, the following figures for ages were obtained

cases fall between thirty and sixty years Of these 85 cases, there were 73 Porto Ricans, 10 Continental Americans, 1 Canadian and 1 Arab While the proportions of Continental Americans to Porto Ricans in the Island is approximately 1 to 50, the former live largely in San Juan, are mostly well-to-do, and a large proportion seek medical care in the single American Hospital The figures, therefore, do not support the prevalent idea that sprue is much more common among new-comers than among native residents The mortality figures of the Health Department, likewise show no

significant differences in the incidence among white and colored

II. Etiology

In any discussion of the question of etiology several questions always arise

(a) Is sprue a sequel to wasting diseases of the tropics? A study of the clinical histories of the 85 Presbyterian Hospital cases with special reference to previous or coexisting infections does not support the idea that sprue is a sequel to infection with bacillary or amebic dysentery, malaria, syphilis, tuberculosis, or to the various helminthic infestations, particularly hookworm. While all of these infections except the dysenteries, are fairly common in Porto Rico, no correlation with sprue is evident when the data are tabulated, the associations with any of these infections being no more frequent than among non-sprue cases (Table II)

Answers of sprue patients to questions as to habits of eating, however,

tend to confirm Ashford's theory that excessive indulgence in sweets, bread-stuffs, rice, potatoes, and greasy foods, such as lard and olive oil, is a contributory factor in the development of sprue (An interesting discussion of the food problem in Porto Rico is contained in a recent article by Cook ) It is significant that 60 of the 85 cases, or 70.5 per cent, were discharged as markedly improved, after treatment with a "sprue diet" consisting of selected types of fats, restricted carbohydrates, and an abundance of proteins and vitamins It has been found that a majority of sprue patients recover normal health on dietary treatment only, without the use of any medication, and that they remain well, if they adhere to the diet Advanced cases showing the so-called "sprue cachexia," however, may not respond

(b) Is sprue a transmissible disease?

An attempt was made to transmit sprue to 3 human subjects, all white

TABLE II  
SHOWING IMPORTANT COMPLICATING DISEASES AND SIGNIFICANT POINTS IN PAST MEDICAL HISTORY OF 85 CASES OF SPRUE TREATED AT THE PRESBYTERIAN HOSPITAL, SAN JUAN, PORTO RICO,—(1925-1928)

<i>Important Complicating Diseases</i>		<i>Significant Diseases in Past Medical History</i>	
Hookworm	7	Typhoid fever	14
Trichuris trichiura	8	Malaria	19
Ascaris lumbricoides	3	Syphilis	8
Cirrhosis of Liver	1	Influenza	11
Tuberculosis (lung and pleura)	6	Tuberculosis	2
Suspected T B	1	Dysentery	2
Cancer of tongue	1	Jaundice	3
Cancer of stomach	1	Rheumatism	7
Ulcer of stomach or duodenum	2		
Pyloric Obstruction	2		
Syphilis	1		
Malarial Cachexia	1		

Porto Rican adults, by rubbing into their tongues the scrapings from the tongue of a cachectic sprue patient who was suffering with very severe diarrhea, marked psilosis of the tongue with aphthous ulcers and atrophy of the papillae, severe anemia, and atrophy of the liver. These attempts, as well as similar experiments on 3 ring-tailed monkeys (*Macacus rhesus*), have been thus far unsuccessful. Three monkeys were also fed with feces from this sprue case. Thirteen human subjects were inoculated intra-cutaneously with various living monilia cultures and monilia psilosis cultures were rubbed into the tongues of three monkeys and three persons. In all cases no symptoms of sprue developed up to six months after inoculation.

### III The rôle of *Monilia psilosis* (Ashford) in sprue

A majority of our sprue cases have shown *M. psilosis* in the feces, but confirming the work of Hines, Fairly and Mackie, and others we have found this organism also in many patients who were not suffering from sprue, and have failed to find the fungus in many typical sprue cases. Blood cultures made in eight cases of sprue also showed no monilia. Contrary to the suggestion of several investigators that monilia proliferate in the intestine because of the increased acidity of its contents, and that the fungi disappear when the intestinal contents become alkaline after feeding a special sprue diet, we have observed that *M. psilosis* grows well in infusion broth at pH 6 to 8, the optimum being at 7. Furthermore, when *M. psilosis* is

planted in tubes of broth of varying pH (5 to 8), the hydrogen-ion concentration of all tubes after a few weeks tends to reach a pH of about 8, thus being the optimum for the survival of this organism.

#### (a) Toxic substances in *Monilia psilosis*

It has been asserted that cultures of *M. psilosis* are more toxic for animals than other forms of monilia. Our experiments have shown that, while *M. psilosis* is more toxic than *M. albicans*, we also find that a monilia-like organism, a cryptococcus from cutaneous blastomycosis, is much more toxic than *M. psilosis*. We have been able to demonstrate an endotoxin in cultures of *M. psilosis* which is attenuated by heating at 60°C for one half hour and retained by a Mandler filter. This endotoxin, as well as many other autolysates, extracts and cultures of this organism shows no hemolytic activity against human erythrocytes in vitro. When grown in human blood broth for several days and filtered through a Mandler candle, *M. psilosis*, *M. albicans* and the cryptococcus show evidence of an extra-cellular toxin. This can be demonstrated only by intra-cutaneous injections into human subjects. These endo- and exotoxins do not, however, manifest any antigenic specificity when tested by the intracutaneous method in a number of sprue patients as well as miscellaneous controls, or in rabbits which had been previously injected with various types of living and killed monilia.

#### (b) Skin reactions in sprue with toxins of various monilia

The exotoxins of the three monilia



cultures together with the corresponding vaccines of Michel (killed, autolyzed suspensions) were tested on a series of 22 undoubted cases of sprue and on 26 patients suffering from various medical and surgical disorders. The results, indicate that while a large percentage (73) of sprue cases gave positive skin reactions to the exotoxins of *M. pilosus*, a still larger percentage (82) of the same series also reacted to the toxins of *M. albicans* and of a cryptococcus of cutaneous blastomycosis. In the control series (non-sprue patients) about 35 per cent reacted to all three types of toxins. The results with the use of killed autolyzed monilia suspensions (Michel vaccines), as antigens, gave similar comparative results, with lower absolute figures. The sprue cases were 55-64 per cent positive, while the control series were 23-27 per cent positive.

(c) *Monilicidal activity of the whole blood in sprue*

With the use of the new technic of Bull and Tao, specimens of whole blood taken from a series of 20 sprue patients were compared with blood obtained from 20 miscellaneous hospital patients in their ability to inhibit the growth of various monilia. We failed to demonstrate any specific monilicidal property in the blood of sprue patients, the power to inhibit the growth of monilia being equally possessed by many blood specimens from non-sprue patients.

These immunological investigations, which will be reported in full in later communications, do not support the hypothesis that tropical sprue in Porto

Rico is caused by a fungus of the species *Monilia pilosus*.

II'. *Are the digestive disturbances observed in sprue patients due to a state of hypersensitiveness to specific food stuffs?*

Since our investigations could not substantiate the infectious nature of sprue, it was considered advisable to test the hypothesis that the untoward symptoms of the disease—diarrhea, sore tongue, tympanites, etc., are due to a state of specific hypersensitiveness to certain food stuffs. The foods which most frequently exaggerate the symptoms of active cases or cause relapses in recovered cases, are rice, wheat-bread, potatoes and fats. We therefore, included these in our list of 32 "allergens" to be tested by the "scratch" or "cutaneous" method on a series of 29 sprue patients and 26 miscellaneous controls. The commercially prepared proteins from the food stuffs most consumed in Porto Rico (beans, pork, rice, bread, cod-fish, potatoes, etc.) were used, as were also some of the purified starches obtained from rice, potatoes, and beans, and certain fats (lard, butter, and coconut oil) as well as a Porto Rican spice (achiote), a native pepper and coffee. No hypersensitiveness to any of these foods was demonstratable.

V. *Biochemical observations on sprue patients*

In the course of routine clinical examinations in the laboratories of the Presbyterian Hospital, (San Juan) it was observed that of 30 sprue cases, only five, or 16.7 per cent, had a total

achlorhydria, ten, or 33 per cent, had hypochlorhydria, while the remaining 50 per cent showed a normal HCl content. In contrast to this, it will be remembered that most investigators report 90-99 per cent achlorhydria in pernicious anemia.

The examination of the blood (Folin's methods) for cholesterol, urea, uric acid, creatinin, chlorides and glucose, revealed no significant findings excepting very low cholesterol figures (1110 and 676 mg per 100 cc of blood) in a case which was markedly cachectic. The sugar tolerance curves and the phenolsuphonephthalein tests of kidney function did not yield any constant results (Table III).

### CONCLUSIONS

1 With 322 deaths registered from sprue in two years and a half and 85 cases treated in a single 70-bed hospital in the same period, the disease must be considered fairly common in Porto Rico. Natives and continental Americans appear equally susceptible, and no marked difference is noted in the incidence among males and females, and among whites and colored.

2 Inoculation of human volunteers with sprue tongue scrapings and with cultures of *Monilia psilosis* has given negative results. Attempts to transmit the disease to monkeys by similar inoculations and by feeding the feces of sprue patients have been likewise negative.

3 While *Monilia psilosis*, suspected of an etiologic role in sprue, contains an exotoxin as well as an en-

dotoxin, these products do not show any hemolytic activity in vitro. Skin tests on sprue patients and controls with exotoxins and endotoxins of *M. psilosis* also fail to show an immunological relationship. Tests with toxins of two related organisms (*M. albicans* and a cryptococcus), not suspected of being related etiologically to sprue, have given similar results. It is also found that the blood of sprue patients exhibits no specific monilicidal activity.

4 Sprue patients give no specific cutaneous reaction (scratch test) to any of 32 local foods, indicating that their intolerance to certain foods is probably not to be explained on an allergic basis.

5 Of the common biochemical methods used in clinical examinations, gastric analysis is of the greatest value in the diagnosis of sprue. The rarity of achlorhydria in sprue is an important point in differentiating the disease from pernicious anemia.

### ACKNOWLEDGEMENTS

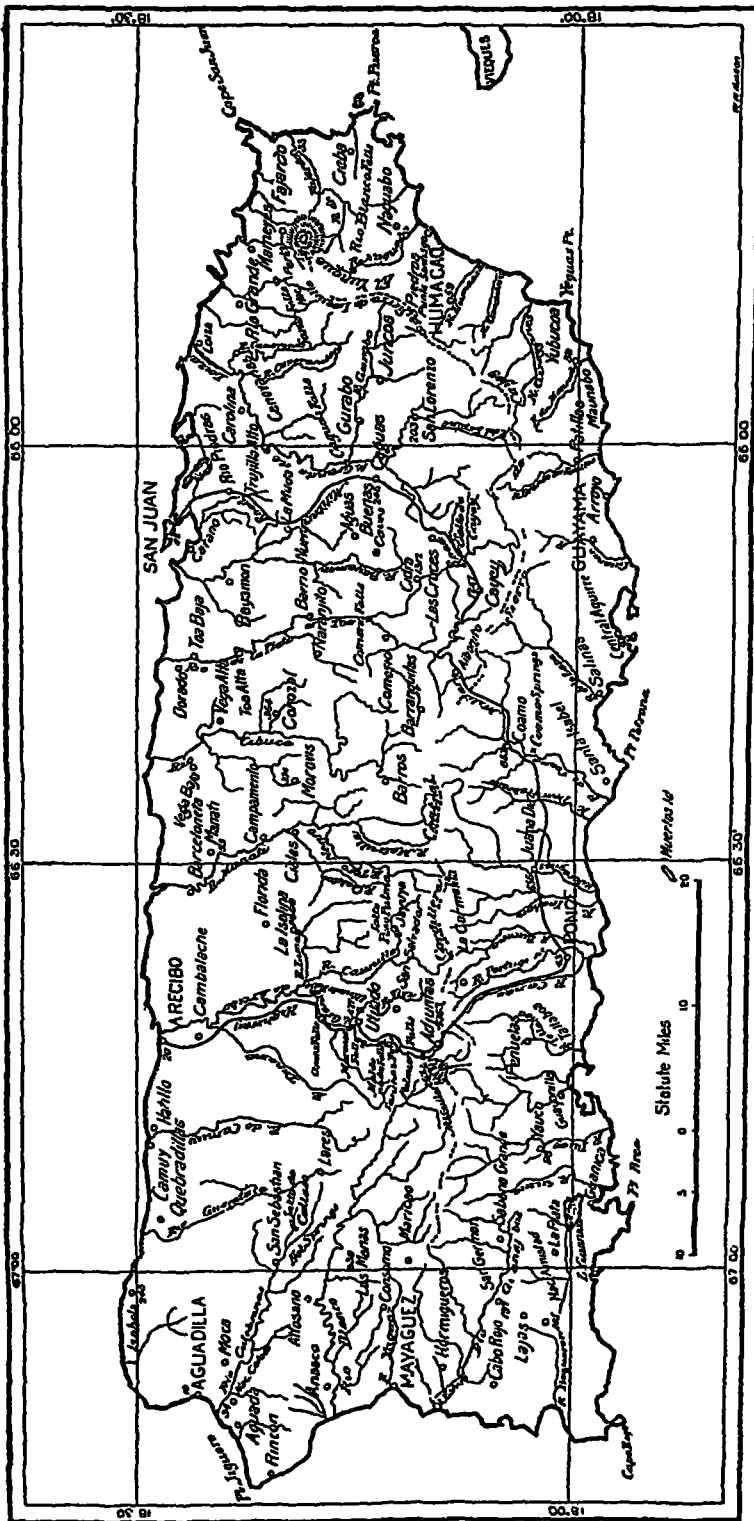
We are indebted to a number of physicians of Porto Rico, particularly Dr Wm R Galbreath, Dr Walter Glines, Dr Gary Burke and Dr Américo Serra of the Presbyterian Hospital, San Juan, for cooperation in carrying out tests on patients under their care. We are especially grateful to Dr B K Ashford for cultures of the several fungi used in the investigations and to Dr Robert A Lambert, former Director of the School of Tropical Medicine for very helpful criticism and advice.

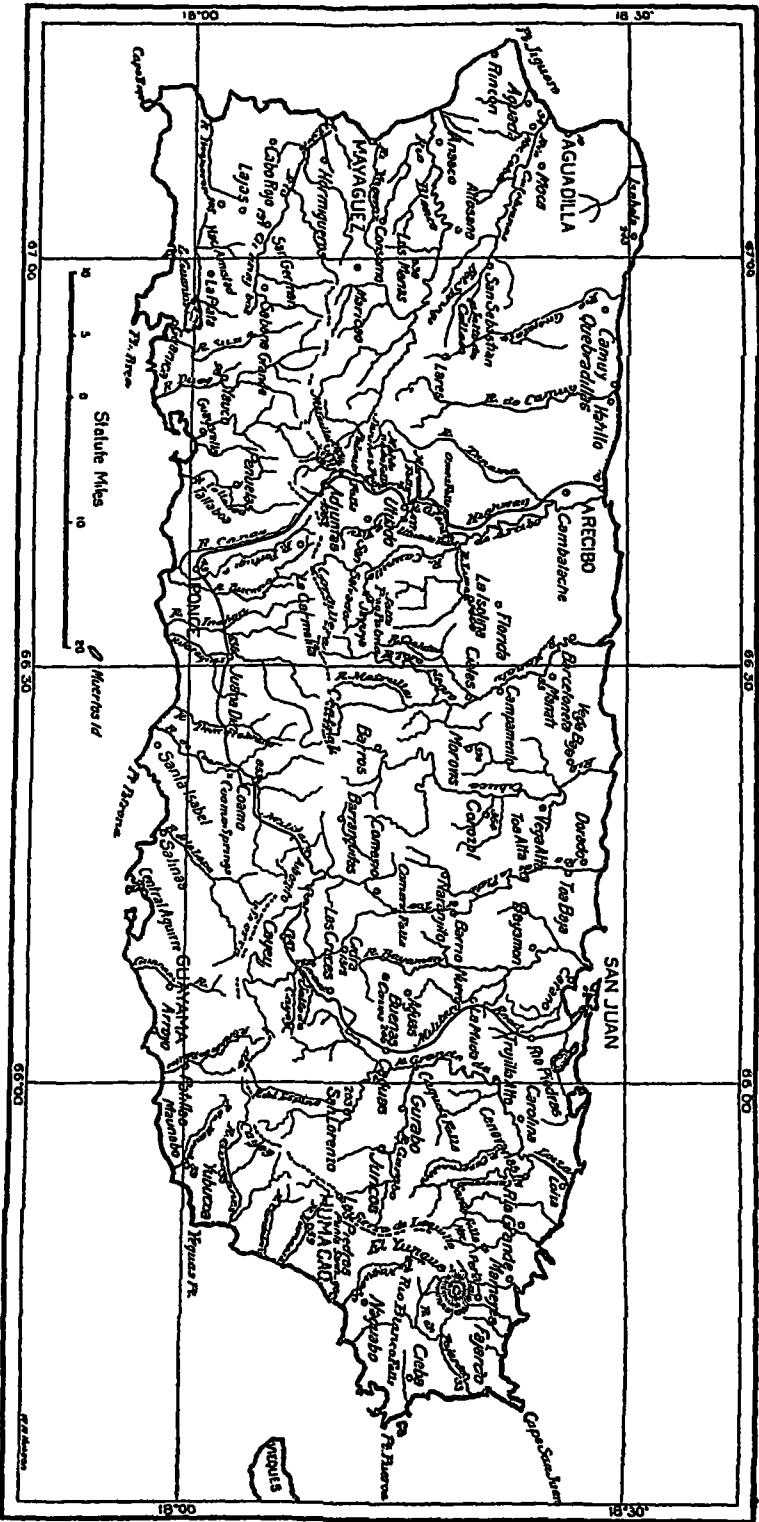
TABLE III  
BIOCHEMICAL OBSERVATIONS ON SPURD PATIENTS

Case	Clinical History	Clinical Exam	Blood	Blood Chemistry	Other Laboratory Tests	Special Exam
1	Weakness, diarrhea, flatulence	Emaciated, cachectic, tongue red glazed and moist small liver, abdomen distended	R.B.C.— 2,410,000 W.B.C.— 3,550 Hbg 70% Polys 58% Lymph 39% Eos 3%	UN UA Cr 18	Icteric Index 460 Chol 168 GI 28 Gastric Analysis (Acidity) Total 300 Free HCL 200 330 450 330 100 200	Glucose Tolerance Test, mg per 100 cc Fasting 825 1st hr 1400 2nd hr 1100 3rd hr 510 4th hr 1070 Monilia absent in feces
2	Duration 4 months, weakness and burning of tongue, loss of weight, diarrhea, Beef and fatty foods disagree	Pale, emaciated Tongue pale, clean raw edges around tip Tenderness of abdomen	R.B.C.— 1,300,000 W.B.C.— 5,800 Hbg. 47% CI—16 Polys 60% Lymph 30% Eos 8% Trans 2% † nucleated R.B.C	UN UA Cr 148	Chl GI 2184 480 1224 Gastric Analysis Free 15 Total 1125 30 775 225 850 40 100 35 850	Monilia absent in tongue and feces Icteric Index 62

17354 10-11-26 49 M W P R Julian Apolinario	Duration 2½ months, sudden onset, epigastric distress, sore tongue, weakness, 12 stools a day, yellowish foamy, mucus, flatu- lence	Tongue raw, clean and smooth, papil- lae absent on tip and anterior, small liver, dehydrated Saccharose aggra- vated 2 children and father have sprue	R B C— 2,420,000 W B C— 5,600 Hbg 65% Polys 38% Lymph 57% Poikilo and aniso	UN U A Cr	168 — 123	Chol G1 N P N	1110 9174 3015	Feces trichu- ris trichura Rosenthal liver function test normal
16924 6-14-26 44 F W P R Ana Maria Ruell	Duration 8 years, diarrhea, dyspep- sia, weakness, pal- pitation and dyspnea, anemia	Weakness, unci- nariasis	R B C— 680,000 to 1,720,000 W B C— 1,200-2,800 Hbg 45% Poikilo and anisocytosis	UN U A Cr	581 — —	Chl G1 N P N	— — —	Feces show Hookworm, ascaris Gastric Analysis Free Total 14 55 56 214 216 302 Occult bld—
17719 1-27-27 59 M W Am (Mr O)	Loss of weight, weakness, diar- rhea, sore mouth, stools 4-8, large, light, frothy, fol- lowing high car- bohydrate diet Treated for gout	Emaciated	R B C— 3,920,000 W B C— 7,300 Hbg 70% Polys 30% Lymph 65% Eos 2% Trans 3%	UN U A Cr	182 — —	Chl G1 N P N	— 795 —	Gastric Analysis Free Total 24 52 52 54 75 72 P S P 1-20% 2-20%

Clinical Exam	Blood	Blood Chemistry		Other Laboratory Tests		Special Exam
		UN	Chl	Gastric Analysis	Monilia present	
Very thin Tongue red and beefy	RBC—	UN	84	—	Monilia absent in feces and tongue	Icteric Index 44
	3,600,000		Gl	—		
	Hbg 86%	UA	24	Free	Total	
		Cr	13	0	75	
				50	175	
Irritated, sore tongue, diarrhea (Carcinoma of pancreas?)	Secondary anemia	UN	140	—	PSP	Monilia present on tongue Icteric Index 457
	RBC—	UA	—	155	1st 35%	
	3,300,000		NPN	357	2nd 30%	
	WBC—			Gastric Analysis		
	7,500			shows no free acid		
	Hbg 60%					
	Polys 65%					
	Poikilo, etc					



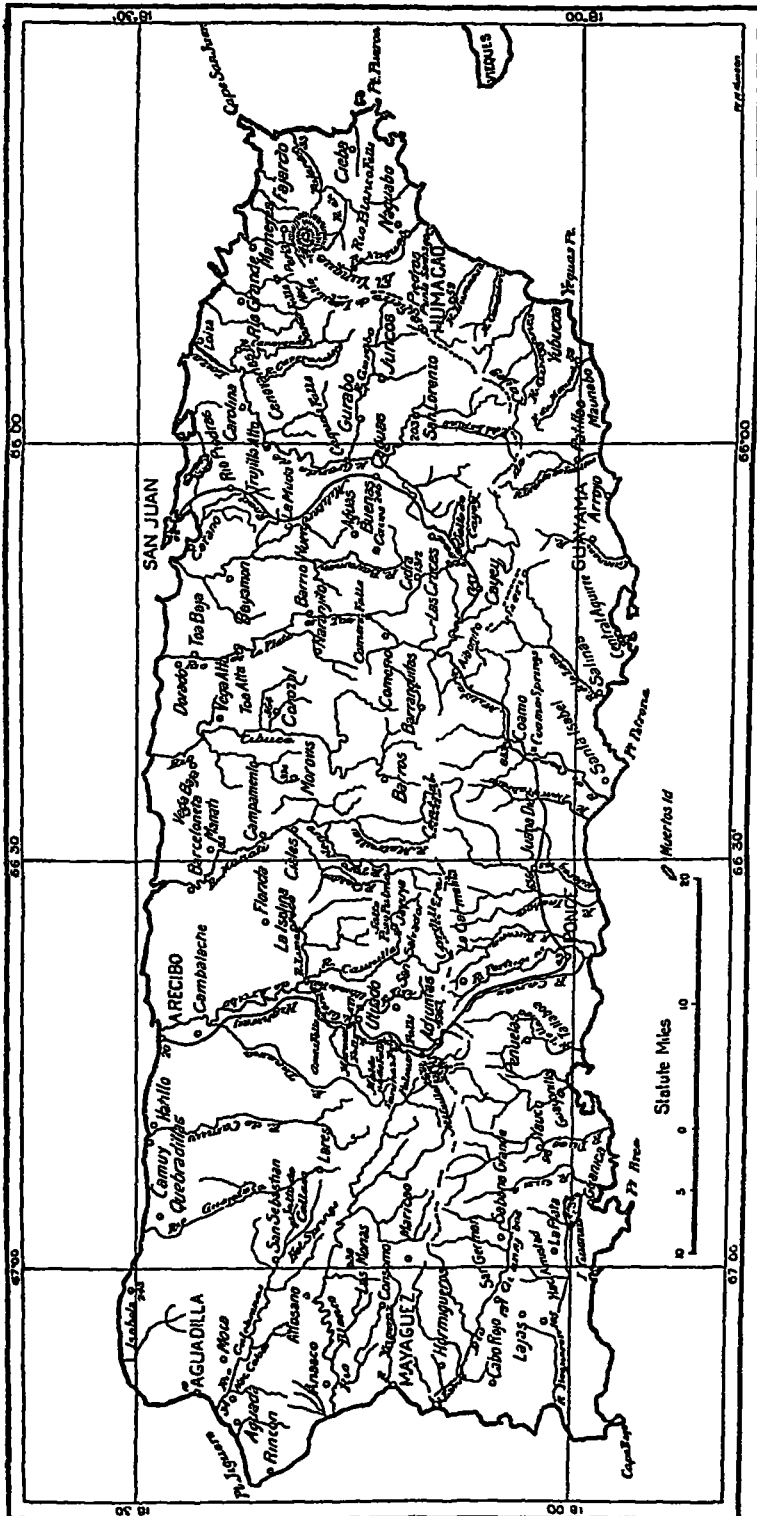


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No	Age, Sex, Color, Name	Clinical History	Clinical Exam	Blood	Blood Chemistry	Other Labora- tory Tests	Special Exam
18721	11-15-27	Diarrhea 4 months, loss of weight (25 lbs), weakness, stools 6 a day, pain and burning in tongue	Very thin Tongue red and beefy	RBC— 3,600,000 Hbg 86%	UN UA Cr 84 Gl NPN 24 13	465 — — Gastric Analysis Free 0 50 175 175 175 200	Monilia absent in feces and tongue Icteric Index 4.4 75 175 325 400 375 40
50 F	W	Duration 3 years Tenesmus, white diarrhea with mucus, loss of weight, severe flatulence, sore tongue	Emaciated, sore tongue, diarrhea (Carcinoma of pancreas?)	Secondary anemia RBC— 3,300,000 WBC— 7,500 Hbg 60% Polys 65% Poikilo, etc	UN UA 140 — Chl Gl NPN 155 357	— 1st 2nd PSP 35% 30% Gastric Analysis shows no free acid	Monilia present on tongue Icteric Index 4.57
A	Saniago						



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# Diabetes Mellitus: A Further Study of the Etiology of the Disease\*

By JOHN C KRANTZ, JR, *Baltimore, Md*

## INTRODUCTION

RECENT literature indicates the existence of a hyperglycemic principle in the blood of diabetic animals. Thus L. Kepinov and S. Petit-Dutailis (1) showed the existence of a principle in diabetic blood which acts antagonistically to the action of insulin. These investigators depancreatized dogs to the extent that a normal blood sugar was just maintained in these dogs the injection of large quantities of diabetic blood produced a hyperglycemia which lasted for several days. Depisch and Hasenohrl (2) found the serum from a case of diabetes with a paranephritic abscess to have an insulin-inhibiting action on rabbits. Serum from cases with diabetes but without sepsis did not show this effect, and cases with sepsis but without diabetes did not show it.

Of special importance is the work of Bergey (3) who has conducted a series of experiments in which he produced glycosuria in rabbits by the intravenous injection of diabetic urine which had been passed through a Berkefeld filter. Serum broth which

was inoculated with diabetic urine and cultivated under aerobic conditions for fifty-six days, was found by this investigator to produce glycosuria when injected into rabbits. Very recently certain other investigators (4 and 5) in this field have failed to observe the infectivity of diabetic urine as noted by Bergey. The present author considered this work of epoch-making importance in the etiology of diabetes mellitus and began a series of investigations, to further substantiate, if possible, the existence of the virus of diabetes, by the phyto-pharmacological method of Macht (6, 7 and 8) and his collaborators.

## EXPERIMENTAL

### 1 *Effect of Intravenous Injections of Diabetic Urine*

Ten rabbits weighing from 1.5 to 2 kilos were fasted for 24 hours, and blood sugar determinations (9) made, and the filtrate obtained, by passing the diabetic urine through a Berkefeld filter, was immediately injected intravenously. Each rabbit received 2 cc of diabetic urine and the controls received 2 cc of normal urine. The urines were obtained from the metabolic laboratory of the Johns Hopkins Hospital. The patients were suffering

\*From the Laboratory of Pharmaceutical Research, Sharp and Dohme, Baltimore, Md

with moderately severe cases of diabetes mellitus, some under dietary control alone and others were using insulin. Three of the four diabetic urines gave a strongly positive reaction with Benedict's solution, whereas the fourth one produced only a very faint green turbidity with the same reagent. The urines gave negative reactions for acetone and diacetic acid. Table I records the results of these injections

of diabetic, as well as normal urine, are very toxic to rabbits and in those cases in which the rabbits survived there was no evidence of hyperglycemia. Through the kindness of Dr. James C. Munch of these laboratories an autopsy was made on rabbit No. 5, which revealed degeneration and cirrhosis of the liver and kidney congestion especially of the cortico-medullary boundary. Having determined the

TABLE I  
Effect of Intravenous Injections of Urine upon the Blood Sugar of Rabbits

Rabbit No	Urine of Patient 2 c c	Fasting blood sugar mgm per 100 c c	Blood sugar 8 days after injection mgm per 100 c c	Blood sugar 16 days after injection mgm per 100 c c	Glycosuria of Rabbit	Days survived after injection
1	E L diabetic	82			—	6
2	E L	87			—	7
3	M T diabetic	76	79		—	12
4	M T	74			—	7
5	J S diabetic	74			—	6
6	J S	87	95	45 the day before death	—	17
7	G W diabetic	82			—	1
8	G W	87			—	7
9	J C normal	98	89		—	
10	J C normal	106	79		—	15

The results recorded in Table I indicate that the intravenous injections

of toxic nature of the intravenous injections of urine, the next phase of this

investigation had for its purpose the study of the influence of subcutaneous injections of diabetic and normal urine

## 2 Influence of Subcutaneous Injections of Diabetic Urine

The fasting blood sugars of five rabbits were determined. Two were injected with a diabetic urine, which had been passed through a Berkefeld filter. Two others were injected with the urine of another patient and the fifth was injected with urine from a normal person. As in the previous experiments these rabbits weighed between 1.5 and 2 kilos and each received 2 cc of urine, in each case injected subcutaneously.

These diabetic urines were obtained from the University of Maryland

Hospital, each patient was suffering with moderately severe diabetes. Each urine gave a strong positive reaction to Benedict's Solution, but was acetone and diacetic acid free. Table II records the results of these injections.

The results obtained by the subcutaneous injections of urine indicate that, although the percentage of rabbits surviving is greatly increased, there is no evidence of these injections producing the cardinal symptoms of diabetes mellitus. It is true that the fasting blood sugar of rabbit No. 14 was somewhat high eight days after injection, but its return to normal seems to indicate that this was a transient hyperglycemia possibly due to fright rather than the typical permanent hyperglycemia of diabetes mellitus.

TABLE II  
Effect of Subcutaneous Injections of Urine upon the Blood Sugar of Rabbits

Rabbit No	Urine of Patient 2 cc	Fasting blood sugar mgm per 100 cc	Blood sugar 8 days after injection mgm per 100 cc	Blood sugar 16 days after injection mgm per 100 cc	Blood sugar 24 days after injection mgm per 100 cc	Glycosuria of Rabbit
14	M K diabetic	128	192	97	111	—
94	M K diabetic	97	113	106	109	—
95	M C diabetic	120	120	74	104	—
64	M C diabetic	109	125	64	114	—
84	J C normal	116	82	died at this time		—

### 3 *Effect of Subcutaneous Injections of Serum Broth Inoculated with Diabetic Urine*

Fifty tubes of serum broth were inoculated with varying quantities of the

Berkefeld filtrate obtained from the urine of three diabetic patients (University of Maryland Hospital) These tubes were cultivated for 56 days and their effect upon the fasting blood

TABLE III

Effect of Subcutaneous Injections of Serum Broth Inoculated with Diabetic Urine  
Cultivated 56 days

Rabbit No	1cc serum broth	Fasting blood sugar mgm per 100 cc	Fasting blood sugar 8 days after injection mgm per 100 cc	Fasting blood sugar 16 days after injection mgm per 100 cc	Glycosuria of Rabbit
2	M C diabetic	104	159	129	—
16	J C normal	84	137	119	—
56	M DeV. diabetic	115	129	127	—
62	M P diabetic	116	119	119	—

TABLE IV

Effect of Subcutaneous Injections of Serum Broth Inoculated with Diabetic Urine  
Cultivated 76 days

Rabbit No	Serum broth 1cc	Fasting blood sugar mgm per 100 cc	Fasting blood sugar 8 days after injection mgm per 100 cc	Fasting blood sugar 16 days after injection mgm per 100 cc	Glycosuria of Rabbit
41	J C normal	114	116	105	—
13	M C diabetic	122	135	104	—
5	M DeV. diabetic	111	116	119	—
94	M P diabetic	111	111	114	—

sugar of rabbits studied. A control of normal urine was prepared also. Table III records the results of these injections.

The results of the subcutaneous injections of serum broth recorded in Tables III and IV indicate that there was no hyperglycemia or glycosuria produced.

#### 4 *Phytopharmacological Experiments*

In order to determine the toxicity of the serum broth inoculated with normal and diabetic urine after 46 days, the cultivation upon the seedlings of *Lupinus albus* the method employed by Macht and his associates, particularly Macht and Rowe (10), was used. These cultures of serum broth were extremely toxic to plant protoplasm, as indicated by the results given in Table V.

The extreme toxicity of these cultures to plant protoplasm made it im-

possible to study quantitatively the relative toxicity of the urines in this medium. A study of Table V indicates that these values (Index of growth of the seedlings) have no quantitative significance, however, it is of interest to observe, that the culture made with normal urine is just as toxic as those prepared with diabetic urine. A more significant phytopharmacological observation was made when the blood serum of rabbits injected subcutaneously with normal urine was compared with the serum of rabbits injected subcutaneously with the diabetic urine.

The result of this experiment is recorded in Table VI.

The results recorded in Table VI indicate that the blood serum of rabbits injected subcutaneously with diabetic urine is no more toxic to plant protoplasm than the serum of those injected with normal urine.

TABLE V  
Phytopharmacological Study of Serum Broth Inoculated with Urine

No		Index of Growth of Seedlings Percentage
1	In Shrive Solution (11)	100
2	Urine of patient, M DeV diabetic, in serum broth, 0.83 per cent conc broth in contact with seedlings	130
3	Same as 2 but 1.7 per cent conc	110
4	Same as 2 but 0.41 per cent conc	300
5	Same as 2 but 2.5 per cent conc	120
6	Urine of patient J C normal in serum broth 0.33 per cent conc broth in contact with seedlings	175
7	Same as 6 but 0.66 per cent conc	18



TABLE VI

## A Phytopharmacological Study of Blood Serum of Rabbits \*

No		Index of Growth of Seedlings Percentage
1	In Shive Solution	100
2	1 per cent Blood Serum of Rabbit 84 injected with normal urine	86
3	1 per cent Blood Serum of Rabbit 94 injected with diabetic urine	84
4	1 per cent Blood Serum of Rabbit 95 injected with diabetic urine	90
5	1 per cent Blood Serum of Rabbit 64 injected with diabetic urine	74
6	1 per cent Blood Serum of Rabbit 14 injected with diabetic urine	76
7	Same as 6	75

\*These phytopharmacological experiments were conducted 18 days after 2 cc subcutaneous injections of urine

## DISCUSSION OF RESULTS

The experimental data correlated in this investigation of a zoological and phytopharmacological nature seem to contraindicate the existence of a diabetic principle responsible for the transmissibility of the disease, by the methods herein described. It is possible, that as the former mentioned investigator (3) obtained glycosuria by these methods, that the presence of glucose in the urine was caused by a lowered renal threshold due to kidney impairment, as no blood sugar determinations are recorded. In no instance was the present author able to produce glycosuria in rabbits by the injection of diabetic urine and no marked permanent hyperglycemia resulted.

## CONCLUSIONS

From the zoological and phytopharmacological experiments herein described, evidence has been produced, which seems to contraindicate the existence of a virus of diabetes which in turn may be responsible for transmissibility of diabetes mellitus.

The author is indebted to Mr C Jelleff Carr for his technical assistance during this investigation.

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# Our Debt to Aristotle

By L. J. MOORMAN, M.D., F.A.C.P.

**T**HREE hundred and eighty-four years before Christ came to Bethlehem Aristotle was a babe in ancient Macedonia. From the womb of Phoestis had sprung the master mind of all ages "The sovereign lord of the understanding." Two and a half centuries before Saint Paul received the call for help in Macedonia, this little kingdom, resting quietly on the fringe of Athenian glory, had sent into the world the first evangel of natural history and the rightful progenitor of all the positive sciences. The author of logical thinking and the stabilizer of metaphysics.

Aristotle was born in the little town of Stagira. He was of Greek lineage. Phoestis, his mother, belonged to Chalcis, where Aristotle took refuge from his enemies during his last days. His father, Nicomanchu, was a doctor, tracing his descent and his art to Machaon, a son of Aesculapius.

The King of Macedonia came to Stagira annually to hunt wild boar and Nicomanchu served as physician for the royal hunting party. Aristotle's mother being dead, he was permitted at a tender age to accompany his father on these difficult and dangerous excursions. It is said that the king became very much attached to Aristotle and was pleased to have him as a companion for his own son Philip. Al-

though Nicomanchu was killed by an avalanche of sliding stone while Aristotle was still quite young, the king continued to include him in his party for the annual hunt, because of his good spirits, his unbounded energy and endurance. It is said that Aristotle declined an invitation to become a resident in the Royal Palace in order that he might go to Athens to study at the School of Plato. However he was destined to enter ultimately the royal court as Alexander's tutor, rather than as a companion to Philip, who was to become the father of the World Conqueror.

At the age of eighteen, in the year 366 B.C., Aristotle came to the Greek metropolis and attached himself to the School of Plato where he remained for twenty years. Plato was then 60 years of age. Socrates was about the same age when Plato became his pupil. Socrates spent his energies redeeming the individual man, while Plato sought to redeem the world. Yet Plato was true to his Socratic teaching in that he "sought truth with his soul." He accepted the simple message of Socrates that "behind every living form there is the divine reality of life itself." Aristotle soon attracted the attention of Plato and as time passed their intellectual differences served to control their affection for each other. In one

breath Plato would refer to Aristotle as the genius of his school and in another he would ridicule him for seeking knowledge in books. These mental differences which separated the master and pupil ultimately divided the world into two camps. The Platonists and Aristotelians.

Aristotle was not a materialist, he believed in God, but his methods of study differed from those of Plato. While Plato contemplated the universe in a mystical, soul-satisfying manner, Aristotle gathered knowledge by reading, by talking with people in all walks of life, especially those having intimate contact with living creatures, and, of greater significance, he acquired knowledge by a close analytical study of living forms. He was a true biologist over two thousand years before Lamarck coined the term "Biology." This method of study was considered an unwarranted innovation and was looked upon with contempt by Athenian Philosophers. Aristotle had not only aroused the criticism of Plato by reading books, but he had brought upon his head the contempt of Athenian culture by descending from the peaks of Platonic teachings to "Grub for knowledge in the base earth of natural history." It must have required courage little short of that exhibited by Socrates for this young student, an outlander from the unpopular court of Macedonia, to pursue his studies and demonstrate his methods in the city of Athens. To literally recall the wandering soul from star-gazing and day-dreaming to the facts of man's earthly existence. We may safely say that Aristotle originated the

systematic study of natural history. In other works, he founded the sciences of comparative anatomy, systematic zoology, embryology, teratology, botany and physiology. He definitely laid the foundation upon which rests all modern scientific research.

While Phillip and Alexander the Great were soon to occupy the center of the world stage because of the invincible march of the Macedonian phalanx, time has proven that the destinies of the human race rested not in the hands of these conquering monarchs, but in the methods of the quiet reader and teacher whose voice was destined to carry through the centuries, penetrating the black night of the Dark Ages to take part in the revival of learning and to guide the progress of science, thereby enriching modern life in innumerable ways, through all the different avenues of scientific study and research. During the twenty years spent in Plato's school Aristotle must have carried his studies in natural sciences far beyond the point where Plato or any other member of the school could have carried him.

When Plato died Aristotle, because of growing prejudices, deemed it wise to leave Athens. He became a member of the Court of Hermias, a former fellow-student, who had become King of Atarneus. He married the niece of his royal friend and possibly anticipated the probability of wearing the crown in case something should happen to the King. Hermias passed by way of the dagger, revolution ensued and Aristotle was relieved of an embarrassing situation when messengers

arrived from King Phillip of Macedonia, Aristotle's former playmate, urging him to undertake the education of Alexander who was then thirteen years of age. This was apparently a most fortunate coincidence for two of the world's greatest characters. It is impossible to say what might have been the result if Phillip had not selected Aristotle as his son's tutor.

Alexander repeatedly gave credit to Aristotle for the various elements of success which were so manifest in his character and Aristotle must have fully realized the importance of the contributions Alexander made to advance the study of natural history. It is easy to trace, through Alexander, Aristotle's influence upon medical history. Aristotle was a student of animal life and he was a great lover of the horse. It seems that he and his pupil Alexander made a special study of the horse and in the course of this study they set up a complete skeleton and Aristotle prepared an essay which served as the last word on the subject for eighteen hundred years, when the genius of Leonardo da Vinci was fired by Aristotle's essay and the serious study of the horse was renewed by dissecting and painstaking drawings. It is reasonable to believe that Leonardo's interest in natural science was largely inspired by Aristotle's influence. Osler refers to him as being "Insatiate in experiments, intellectually as greedy as Aristotle." In discussing the great anatomists and the keen students of the human form, Osler further says "But greater than any of these and antedating them is Leonardo da Vinci, the one universal genius

in whom the new spirit was incarnate, the Moses who alone among his contemporaries saw the promised land."

In the year 335 B. C., soon after the death of Phillip, Aristotle returned to Athens and established his famous school in the grove of Apollo, favorite haunt of Socrates. Here he spent the most fruitful years of his life, teaching and collecting manuscripts, maps and objects to illustrate his lectures, especially those on natural history. It is said that Aristotle had the first zoological garden and the first museum of natural history in the world. Alexander is said to have given him eight hundred talents to enable him to form this collection and to have laid all the hunters, fowlers and fishermen of the Macedonian Empire under injunctions to report to Aristotle any matters of scientific interest that they observed.

The first of the world's great libraries was here established and those of Alexandria and Pergamon followed. With the exception of Alexander's contribution toward Aristotle's scientific studies, his one lasting accomplishment is Alexandria and it may be truthfully said that the building of this great city and center of learning was a monument to Aristotle's influence in the life of the world conqueror.

After referring to Vesalius, who was born in 1514, as the real father of anatomy, Doctor W. W. Keen says, "If we wish to see its starting-point, we must go back to ancient times—we must retrace our steps to the third century before Christ and transfer ourselves from the amphitheatre of

Padua to that of Alexandria, to discover the bold innovators who first forced the dead human body to disclose its secrets for the benefit of the living." These innovators were Herophilus and Erasistratus who, indirectly through the influence of Aristotle, dissected not only the dead human body but the living as well, in order to search for the hidden springs of life. For centuries the study of anatomy was centered in Alexandria and in the second century after Christ Galen was compelled to go from Pergamus to Alexandria in order to see a skeleton. The dissection of the human body disappeared from the face of the earth for a period of twelve centuries. In Alexandria, this ancient stronghold of science, where tardy tolerance first permitted the dead body to yield to the hand of the investigator its anatomic secrets, Clot Bey, seventeen centuries after dissection had been discontinued, attempted to demonstrate anatomy by the use of the dead body and while in the act of opening the thorax was stabbed by one of his own students, evidently acting under the urge of an insane prejudice against the mutilation of the human form.

We might cite many examples of Aristotle's influence as manifested either directly or indirectly, but we must hasten to consider briefly the specific relation of his life and work to the development of medicine. According to Voltaire his recorded studies on animal life formed the best book of antiquity. While Aristotle stood among the first in intellectual attainments, swaying as he did the domains of logic, psychology, ethics, meta-

physics, rhetoric, poetry and politics, he was far ahead of his time in the study of natural history. In Darwin's "Life and Letters" we find this statement, "Linnaeus and Cuvier have been my two Gods, though in very different ways, but they were mere school boys to old Aristotle." Aristotle mentions five hundred different animals. Some of his references are worthless, but many of them show a minuteness and accuracy of knowledge which could have come only through the most careful and thorough study. We find that he dissected fifty different kinds of animals and there is sufficient evidence to warrant the belief that he dissected the human embryo. He describes in a comprehensive way the development of the embryo chicken and detected on the fourth day the presence of the heart "beating and moving as though endowed with life." He accurately stated many facts in natural history which were overlooked by other observers for centuries. He was not only the first to collect on a large scale the available information concerning the animal species, but he was the first to undertake their classification. His main divisions are the sanguineous and the bloodless animals, corresponding to our vertebrates and invertebrates. While he realized the difficulties of classification, he did his work so well, there was no further advance in this direction until the time of Linnaeus in the eighteenth century.

Aristotle's discussions of anatomy and physiology show breadth of knowledge, which is astounding when considered in the light of the age in

which he lived His discourse on the determination of sex is a magnificent analysis After overthrowing the theories of Empedocles, Democritus and Hippocrates, he presents a theory which though absurd in certain of its phases, has the virtue of placing the determination of sex at the very beginning of embryonic development In this respect Aristotle was 2200 years in advance of modern science In a discourse of the qualities by which the parts of animals differ we are astonished to find him discussing the fluctuating characters with something of the same understanding which Mendel applied over two thousand years later

Sedgwick recently undertook to prove that every mother can nurse her baby and his method of milk expression has been heralded to the world as a most useful discovery Twenty-two hundred years ago Aristotle stated that "cases have been known where women advanced in years, on being submitted to the process of milking, have produced milk and in some cases in sufficient quantities to enable them to suckle an infant"

In discussing nutrition of the animal body, Aristotle, after describing the stomach and intestines, says there must be something to receive the nutriment from these organs and states that "This something is furnished by the blood-vessels which run throughout the mesentery from its lowest part right up to the stomach" Though the world waited nearly two thousand years for Harvey to prove the circulation of the blood, Aristotle was not far from the truth when he writes,

as follows "It is but rational that the flow of blood should extend, as it does, throughout the whole body", and again after describing the water-courses in the gardens, he says, "Now just after the same fashion has nature laid down channels for the conveyance of blood throughout the whole body" The following quotations furnish convincing evidence that Aristotle gave serious attention to the blood and its movement in the body "Blood beats or palpitates in the veins of all animals alike all over their bodies, and blood is the only liquid that penetrates the entire frames of living animals, without exception and at all times, as long as life lasts" If blood is removed, or if it escape in any considerable quantity, animals fall into a faint or swoon, if it be removed, or if it escape in an exceedingly large quantity, they die If the blood gets exceedingly liquid, animals fall sick; for the blood then turns into something like ichor, or a liquid so thin that it at times has been known to exude through the pores like sweat In some cases blood, when issuing from the veins, does not coagulate at all, or only here and there Whilst animals are sleeping the blood is less abundantly supplied near the exterior surfaces, so that, if the sleeping creature be pricked with a pin, the blood does not issue as copiously as it would if the creature were awake" Aristotle considered the heart the center of the sensory, the motor and the nutritive faculties Perhaps next in importance he considers the brain, in his words, "The head has also been chosen by nature as the part in which to set some of the senses"

Aristotle was evidently a close student of the diseases of the human body and their pathology. This is proven not only by frequent references found in his extant works on natural history, but by the fact that he refers to his own treatise on the Principles of Diseases. However, if such a treatise was written, history has left no record of it. The following serve to illustrate his numerous references to diseases and pathology: he discussed somewhat in detail hemorrhages from the wind pipe, stones in the gall bladder, kidneys and urinary bladder, intestinal worms, hydrophobia and diseases of the heart, revealing a comparative study of the heart in animals dying of disease and animals killed for sacrificial purposes. Discussing the bites of serpents, he refers to the asp and says, "The so-called septic drug is made from the body of the animal, and is the only remedy known for the bite of the original." This might be considered a crude anticipation of the present method of treatment with antivenom. He refers to the human kidney as a lobulated organ and advances this as a reason for the incurability of Bright's disease over two thousand years before the name was supplied. This reference to the kidney as a lobulated organ further substantiates the belief that Aristotle dissected the human embryo. He was fairly familiar with the problems of nutrition and recognized the evils of obesity.

In giving advice to Alexander, Aristotle displays an amazing sense of sanitary science. After cautioning against idleness and overwork he makes this startling statement: "Do

not let your men drink out of stagnant pools—Athenians, city born, know no better. And when you carry water on the desert marches, it should be first boiled to prevent its getting sour." This advice antedating typhoid vaccine twenty-three hundred years might have worked well at Chickamauga. It showed clearly that Aristotle recognized that the chief foe of an army may reside in its own camp, or that disease may exact a heavier toll than war itself. The efficacy of his principles is supported by the fact that Alexander's losses were chiefly in men killed on the field of battle.

In "De Parva Naturalia" Aristotle gives the following conception of the scientist and the physician: "But health and disease also claim the attention of the scientist, and not merely of the physician, in so far as an account of their causes are concerned. The extent to which these two differ and investigate diverse provinces must not escape us, since facts show us that their inquiries are, at least to a certain extent, conterminous. For physicians of culture and refinement make some mention of natural science, and claim to derive their principles from it, while the most accomplished investigators into nature generally push their studies so far as to conclude with an account of medical principles." Virchow in "Die Cellular Pathologie" was merely recognizing the efficacy of Aristotle's methods when he said, "We are in the midst of a great reform in medicine. In our day for the first time the full domain of this so comprehensive field of learning has been laid open to scientific research. Doctrines



that belong to the oldest traditions of mankind are put to the test not only of experience, but of investigation. For experience proofs are demanded, for research accurate methods."

Aristotle had an abiding passion for truth. It was this that strained his position with Plato. While his love for Plato was great, his love of truth was greater. In spite of his commanding genius, his theories often fell hopelessly short of the mark and many times he wandered far from the object of his affections. Fortunately, science was not dependent upon the accuracy of his theories, but upon the method

of his procedure, its foundation stands securely upon what he did and not upon what he thought. Aristotle was repeatedly guilty of thinking wrongly, but he never committed the crime of thinking indifferently. As a memorial for Aristotle and an inspiration for us, I have chosen the words of Maurice Maeterlinck, "Our dead are greater and more truly alive than we are, when we forget them, it is our whole future that we lose sight of; and when we fail in respect to them, it is our immortal soul that we are trampling under our feet."

## Editorial

### MORBUS CAERULEUS

The phenomenon of cyanosis of the skin and mucous membranes, usually spoken of as *Cyanopathia* or *Morbus Caeruleus*, associated with certain cases of congenital heart disease, has long been a problem about which much discussion has been waged and varying views have been offered in explanation of its etiology. The oldest of these views is that of de Senac (1749), who advanced the theory that the cyanosis is due to a mixture of venous and arterial blood. Supported by Gintrac, Corvisart and many other authorities, this view has been refuted by Peacock and others, on the ground that cyanosis is not always present in cases in which there is a free mixture of venous and arterial blood. In some of the cases of the most severe type of congenital cardiac lesions, in which there was complete mixture of arterial and venous blood, such as *cor biatriatum triloculare* and persistent *truncus arteriosus*, cyanosis has been absent. Nevertheless Senac's theory is still applied to the explanation of *cyanose tardive*, a terminal cyanosis occurring in septal defects and patent ductus arteriosus, due to alterations in pressure causing a flow of venous blood from right to left through the defect into the arterial stream. This anomalous venous current into the arterial circulation is regarded by Abbott as the chief cause or the essential factor in the great

majority of cases of *morbus caeruleus*. In 1761, Morgagni advanced the theory of venous stasis in explanation of congenital cyanosis. Supported by Louis and Peacock, this view has been widely accepted, although failing to explain the situation completely. The absence of edema and anasarca in the majority of cases of the *morbus caeruleus*, the late appearance or absence of the cyanosis in pulmonary stenosis, made it seem very probable that some other cause in addition to mechanical venous obstruction must operate to produce the cyanosis. Cases reported in the literature of pulmonary stenosis with closed septa, with no opportunity for a venous-arterial shunt, that showed no cyanosis at all, or only a slight degree, even in adult life, provide further evidence against venous stasis as a factor in the production of congenital cyanosis. With the theories of mixture of arterial and venous blood and venous stasis regarded as inadequate to explain the etiology of *morbus caeruleus*, modern writers upon the subject have accepted the theory of deficient aeration of the blood as the essential factor in the production of cyanosis, whether produced by the direct flow of venous blood into the arterial stream or by obstruction to the flow of venous blood to the lungs. Abbott regards the matter as fully settled, that congenital cyanosis depends upon deficient oxygenation, that the

circulation can evidently accommodate itself to a certain degree of oxygen unsaturation, whether brought about by venous stasis, mixture of venous and arterial blood, or by a general slowing up of the whole circulation, but that as soon as this oxygen unsaturation reaches a certain limit, this becomes insufficient for the needs of the body and cyanosis results. Certain secondary factors, such as dilated peripheral capillaries, dark color of the skin, and polycythemia may serve to increase the degree of discoloration, but these factors she regards as concomitant and not primary etiologic factors. In complicated cardiac defects probably all of these factors combine to produce the characteristic mulberry hue and the respiratory symptoms of typical morbus caeruleus. She bases this conclusion upon the monograph of Lundsgaard and Van Slyke on cyanosis. With the principle, that cyanosis is produced by an increase of the reduced hemoglobin in the capillary circulation above a definite threshold value (67 per cent), as the basis for the explanation of its occurrence, these authors classify the possible causes of such an increase into *Modifying factors* which may alter the threshold value of oxygen unsaturation at which the visible manifestations of cyanosis may appear, but which in themselves cannot produce such an increase, as thickness or pigmentation of the skin, altered color of the plasma, raised hemoglobin content of the blood, and variations in the number, size and extent of the capillaries of the skin; and *influencing factors*, which directly produce cyanosis by raising the oxy-

gen-unsaturation of the capillary blood above its threshold value. These determining factors may act in two ways, either by lessening oxygenation in the lungs or by increasing oxygen consumption in the tissues, and there are four of these causative factors. Lessened oxygenation in the pulmonary alveoli, a right to left shunt of venous blood into the arterial stream, an increased reduction of oxygen in the tissue capillaries and the total hemoglobin content. This fourth factor cannot produce oxygen unsaturation in itself, but is of importance in raising this to the threshold value in the presence of any of the other causes. Thus, when the hemoglobin content is very low as in severe anemia, cyanosis will not appear until the oxygen-unsaturation has been raised far beyond its normal threshold value, and when the hemoglobin is very high, as in marked polycythemia, a considerably lower content of reduced hemoglobin will result in the appearance of cyanosis. Lundsgaard and Van Slyke's work has been of great value in the problem of congenital cyanosis in distinguishing the essential causative factors from the modifying ones, and by the graphic presentment of their relative threshold values and combined significance. The modern theory of morbus caeruleus as recognized by Abbott in her chapter on Congenital Cardiac Disease in the last edition of Osler's Modern Medicine combines the essential principles of both the old theories of Senac and Morgagni. The oxygen-unsaturation of the capillary blood corresponds to the mixture of venous and arterial blood of the Senac

theory, while the marked filling of the capillaries corresponds to the Morgagni view that the cyanosis is peripheral. Abbott fails, however, to recognize sufficiently the important recent work on capillary morphology and pathology bearing directly upon the question of morbus caeruleus, just as Lundsgaard and Van Slyke have failed in recognizing the significance of the morphologic capillary picture in cyanosis. The histologic study of the capillary dilatation in morbus caeruleus has been made by Chouppe, Varicot and Gamfert, and the study of the same condition by means of the capillary microscope has been carried out by Janzen, Rominger, Frontali and Redisch and Rosler. LeBlanc has demonstrated that for the appearance of cyanosis in the skin or mucous membranes the thickness of the blood layer in the capillaries is an essential factor. In normal capillary width blood rich in reduced hemoglobin appears still red, but in dilated capillaries blood poor in reduced hemoglobin appears blue. Redisch and Rosler find the capillary-microscopic picture specific for the morbus caeruleus. Paraphrasing their description, on a dark-red background arranged in many layers the capillary loops appear very large as a whole, but especially thickened at their curves and in the venous arm of the loop. The capillaries are many times interwound but less tortuous. In a striking number of the capillaries there is stasis, in others a corpuscular stasis with slightly slowed current. In the upper layers especially there are fine, less drawn-out, scarcely wound loops, which are interpreted as newly-

formed capillaries. There exists, therefore, according to the capillary microscope a condition of the most marked capillary hyperemia with especial involvement of the venous limb of the capillary, with a tendency to stasis of the capillary circulation and the formation of new capillaries. This picture stands out well differentiated from that of the capillaries in cases of cardiac decompensation. There is found in morbus caeruleus and only in it the capillary picture described above. In common with Pachoni, Redisch and Rosler believe that this capillary condition is the chief cause of the extreme cyanosis of morbus caeruleus, it is specific for this condition but it is to be regarded as a secondary symptom of severe congenital cardiac lesions. It is easily diagnosed in life, and may best be designated as "congenital capillary dilatation." Two questions naturally arise in connection with the specific capillary picture of morbus caeruleus, its relationship to the occurrence of drumstick toes and fingers, and to the problem of cyanosis in general. In eight cases of morbus caeruleus with typical capillary picture and cyanosis of high degree, drumstick fingers and toes were present in all, in five other cases of drumstick fingers there occurred four times the capillary picture of cardiac decompensation and in one case a normal capillary picture. It is, therefore, evident that drumstick fingers and toes do not possess a characteristic capillary picture. Pachoni is really the father of the idea that the chief factor of the cyanosis in congenital cardiac lesions is the *congenital capillary dilatation*.

Through the abnormal cardiac function of the fetus, with the resulting stasis, there occurs a disturbance of development in the most distant capillaries showing a fetal structure. No changes in the capillary circulation are to be expected in septal defects owing to the equal pressure in the two ventricles. Still less will they occur in open ductus Botalli, which represents the normal fetal circulation. The occurrence of cyanosis in these cases presents no specific capillary picture, but only that of cardiac decompensation. Pachon<sup>1</sup> also believes that the cases of "cyanose tardive" can also be explained by his theory. If in extra-uterine life the circulatory difficulty becomes lessened or disappears, the conditions for the abnormal capillary dilatation are still present, and there arises a condition of latency. Pachon<sup>1</sup> does not exclude the possibility that after birth changes occurring in the capillaries of the skin may lead to cyanosis. Further, after birth the already prepared capillary accommodation may become greatly increased. The organism has three possibilities of compensation for the circulatory difficulties attending congenital cardiac lesions, the dilatation of the developing capillaries, the new-formation of capillaries and the increase of the canals of Hunter (intercapillary anastomoses). The accommodation capacity of the capillaries lasts throughout early childhood, even up to puberty. This point of view is also of great significance in regard to cyanose tardive. Should the accommodation capacity of the capillaries become insufficient there will take place stasis and

blocking of the capillaries leading to the production of the picture of morbus caeruleus. In this connection the increased circulatory demands and the increase of venous pressure due to the erect position of the body, especially in the extremities of the body, and the essentially increased difficulty of emptying the capillaries towards the venous limb must play an important rôle in the production of a delayed cyanosis. According to Redisch and Rosler, Weiss and Lowbeer, morbus caeruleus cannot be explained on the ground of a quantitatively increased cyanosis, as held by Lundsgaard and Van Slyke. According to Redisch and Rosler no case of morbus caeruleus occurs without the characteristic capillary picture described above—that is dilatation of the venous limb and slowing of the stream. Redisch and Rosler have also been the first to describe a characteristic capillary picture occurring in two cases of stenosis of the isthmus of the aorta. The capillaries of the upper extremities were lengthened, and the venous limb greatly dilated, and the current slow. At the elbows there were multiple capillary aneurysms. The capillaries of the lower extremities, on the other hand, were exceedingly fine and delicate without aneurysmal dilatations. In isthmus stenosis of the aorta there is a marked difference in blood pressure between the upper and lower halves of the body. In the two cases described the blood pressure in the lower extremities was definitely below normal. Whether the total mass of blood in the lower extremities was less than that in the upper could not be determined. In

both cases the legs were well developed and functionally capable, there was no evidence of claudication, in spite of their paleness and coolness. The condition of the capillaries is only the expression of the relative anemia of the legs and lowered blood pressure due to the aortic stenosis. The question of the multiple formation of capillary aneurysms in the upper extremities is an interesting one, since as a rule they are regarded as an affection involving the whole vascular system, due to a vasoneurotic diathesis, lues, atherosclerosis or other severe vascular lesion. Redisch and Rosler have greatly advanced the use of the capillary microscope in the study of circulatory disturbances by their observations. An entirely new aspect is given to morbus caeruleus by their findings of a constant capillary dilatation which they conceive to be the cause of the affection, and by their demonstration that it stands in no relationship to the production of drumstick fingers. The capillary picture discovered by them in isthmus stenosis of the aorta will prove to be a valuable diagnostic sign, if confirmed

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### *THE BOSTON MEETING*

The most successful Clinical Week ever held by the College was that just closed in Boston. With a registration running in the neighborhood of fifteen hundred there was a remarkably full attendance at each session, even up to the last one. The program for the afternoon and evening meetings presented a rich variety of timely and interesting subjects, and was carried through in an eminently business-like

manner. Much praise was heard of the clinical presentations, and for once the clinics may be said to have measured up fully to the expectations of the visiting Fellows and Associates. The arrangements at the Statler Hotel were ideal, and the College owes its thanks to the Management for such efficient cooperation. There was not a single slip-up. The Annual Dinner was most successful, the Ball Room being filled to capacity, and the guests were greatly entertained by the amusing characteristic speech given by Dr Vincent. An unusually large number of Fellows and Associates were inducted into the College at the Convocation. The impression given by this meeting was that the College has fully arrived, that it has become a great institution in the medical forces of this country, and that it can go on now fully established and entrenched in its work and purpose to the greatest success and accomplishments. It has shown that it fills a definite place among the medical societies of the country, that it occupies a unique position in service and function, and that as a factor in the post graduate medical education of the internist it occupies the highest place. No one attending this meeting can have the slightest doubt of the tremendous success achieved by the College. The character of the membership as constituting the most representative internists of the country is very impressive. To the out-going President, Dr C F Martin, of Montreal, is due the sincere thanks of the organization for his labors in advancing the aims of the College. Filled with the highest ideals of what the College should stand for, and what it

should represent, he has during his term of office done much to perfect its organization. The College is also greatly indebted to the Boston physicians who contributed so much to the success of this meeting, and particu-

larly to their most efficient General Chairman, Dr James H Means, whose untiring energy played a very great part in the accomplishment of the most perfect Clinical Week the College has yet seen.

# Abstracts

*Hemorrhagic Glomerular Lesions Produced by Filtrates of Streptococcus Viridans Cultures* By Arnold R Rich, John H Bumstead and Martin Frobisher, Jr (Proc of the Soc for Exper Biology and Med, February, 1929, p 397)

It is well known that hemorrhagic glomerulonephritis occurs with great frequency in association with *Streptococcus viridans* infections, especially with endocarditis caused by this organism. The glomerular changes in the latter affection are generally regarded as a direct result of damage caused by minute emboli from the vegetations on the heart valves. This explanation was doubted by the workers named above for the following reason. If the nephritis associated with *Streptococcus viridans* endocarditis is merely the result of emboli, one might reasonably expect to encounter a similar nephritis quite as commonly in every form of endocarditis characterized by profuse, friable vegetations, regardless of the etiology. But this is not the case. There is no relation between the size of the valvular vegetations and the occurrence or degree of nephritis. The writers have observed florid hemorrhagic nephritis in association with gonococcal endocarditis, in which the vegetations were confined to the right side of the heart, and in which therefore the capillary bed of the lungs would act as a filter for emboli escaping from the vegetations. It may be remarked that gonococcal endocarditis resembles *Streptococcus viridans* endocarditis in the extraordinary frequency with which it is accompanied by hemorrhagic nephritis. A microscopic study failed to convince that the damage to glomerular tufts in the nephritis associated with *Str viridans* endocarditis is necessarily dependent upon the presence of emboli. The glomerular damage differs in no way from that observed in cases of nephritis in which emboli could have played no rôle. It seemed possible that the high incidence of nephritis

occurring in association with certain forms of bacterial endocarditis might be referable to the action of toxins produced by the microorganisms in question, rather than to emboli. Experiments were, therefore, carried out with a strain of *Str viridans* obtained from the blood of a patient suffering from a typical subacute endocarditis with evidences of renal involvement. They were able to produce glomerular damage in rabbits by the intravenous injection of bacteria-free filtrates of fresh broth cultures of this organism. The sterility of the filtrates was always proven by culture. The amount of filtrate injected varied between 2 and 20 cc, and the animals were killed on the day following the injection. There was no definite relation between the amount injected and the degree of renal injury produced. Some unexplained individual susceptibility played a greater rôle. Realizing the sources of error involved in the interpretation of apparent cellular alterations in the glomerular tuft, they regarded as positive only these cases in which actual hemorrhages occurred into Bowman's capsule and the convoluted tubules. The hemorrhages visible at autopsy in the gross varied in number from only one or two to a profuse peppering of the cortex of each kidney. Microscopically, the hemorrhages were always in Bowman's capsule or the tubules, never in the interstitial tissue, and in all instances the escaped blood was perfectly fresh in appearance. In no case did the control injections of broth alone affect the kidney. Spontaneous hemorrhagic glomerulo-nephritis in the rabbit is mentioned extremely rarely in the literature. The investigators have never encountered it in the study of the kidneys of hundreds of rabbits killed for other purposes during the past several years, and their control series of 9 rabbits were free from it. They feel therefore, convinced that the present experiments demonstrate clearly that in the Berkeley filtrates or broth cultures of a patho-



genic strain of *Streptococcus viridans* there is something which can produce glomerular damage in the rabbit. As far as they are aware this is the first time that a condition comparable to acute hemorrhagic glomerulonephritis has been produced experimentally by means of a bacterial filtrate. Whether they are dealing with a true toxin cannot yet be stated. There is evidence, however, that the renal damage in their experiments has nothing to do with allergy. Efforts to concentrate the toxic principle of the filtrate, and so to obtain, possibly, a higher percentage of instances of renal involvement have not yet been successful. No explanation can be offered for the differences in individual susceptibility to the injurious substance in these experiments. In a limited number of experiments in which filtrates of cultures of other bacteria were injected, no renal changes were produced.

*The Experimental Transmission of Leukemia in Mice* By Maurice N Richter and E. C. MacDowell (Trans Soc for Exper Biol and Med, February, 1929, p. 362)

The only report in the literature of the successful transmission of leukemia in mammals is that of Snijders, who succeeded in transmitting the disease by the inoculation of emulsions of tissues from spontaneously affected guinea pigs into normal animals of the same species. Unsuccessful attempts to transmit leukemia in mice were made by Haaland and Tyzzer. In a strain of mice designated as C58, which had been inbred by brother-sister matings since 1921, it was observed that a considerable number of those that lived more than 8 months had enlargements of their spleens and lymph nodes, which on microscopic examination were shown to be due to lymphatic leukemia. Tumors other than those occurring as part of the leukemic symptoms are uncommon in this strain. Saline emulsions of spleens from 6 mice spontaneously affected with lymphatic leukemia were inoculated intraperitoneally and subcutaneously into non-leukemic mice from the same and also from other strains. The non-leukemic mice were young animals of both sexes, from 1

to 2 months old. Following inoculation there appeared in each of the 6 experimental animals enlarged lymph nodes and spleens, with masses or nodules of lymphoid tissue in the abdominal cavity, sometimes forming large tumor-like growths in the mesentery, around the kidneys or along the genital tract. Subcutaneous nodules, enlargements of superficial lymph nodes, mediastinal growths, and fluid in the peritoneal or pleural cavities were also frequently observed. Microscopically, these growths consist of lymphoid cells in a delicate stroma. Many cells are in mitosis and there is infiltration of surrounding structures. Infiltration of the liver, pancreas or lung is common. In some of the inoculated mice there was a striking increase in the number of circulating white corpuscles. The highest count recorded in the experiments was 262,000 per cm., about 3 weeks after inoculation. The increase in cells was due to an absolute and relative increase in the number of lymphocytes, many of which were immature. In some instances, small numbers of abnormal cells were observed in the blood even when the total white count was normal. Similar changes have resulted from the inoculation of emulsions of these experimentally produced lymphoid enlargements, and the condition has been successfully transmitted through several experimental passages. One line has now reached the sixth transfer. Of 110 mice of strain C58 that lived more than 10 days after inoculation, 36 are still alive, and 74 have died or been killed. Of the latter, transmission was successful in 56, unsuccessful in 10, while diagnosis is not yet complete in 8. Fourteen animals of other strains which lived more than 4 days after inoculation with the same material, have had neither lymphatic enlargements nor leukemic blood pictures. Thirteen are still alive, one died but presented no lesions resembling leukemia.

*Studien über den Arteriellen Tiefdruck (Hypotomie) Zu Frage der Beziehung zwischen Blutzuckerspiegel und Blutdruckwert* By Dr Franz Kisch, (Klin Wochenschr, 26 February, 1929, p. 400) That there exists a relationship between hyper-

glycemia and hypotonia has been the subject of much discussion. Observations by Joslin indicate that in diabetics over 35 years of age the blood pressure is higher than in normal individuals. With this Hitzenger agrees, placing the percentage of cases of high blood pressure among diabetics as 46 per cent. Maranon also is of the opinion that diabetics are more inclined to high blood pressure than non-diabetics of the same age. Kylin estimates the number of cases of hypertonia among diabetics as 39 per cent, Rosenbloom at 22 per cent, Perse at about 25 per cent, Strauss at 33 per cent. Ernst Wiechmann estimated the blood pressure in 256 diabetics and found a higher per cent of cases with high blood pressure than in normal cases. Rosenbloom found high blood pressure in diabetics only in cases complicated with aortitis, arteriosclerosis, nephritis, cardiac hypertrophy or aortic insufficiency. Barach found high blood pressure only in those diabetics who had at the same time arteriosclerosis or nephritis. Koopman affirms that young diabetics show a normal blood pressure, while in older patients high blood pressure is the rule. A Friedländer, on the other hand, holds that diabetes scarcely influences the blood pressure. Kisch studied the blood pressure in 463 diabetics (292 males, 171 females) in the age-limits of 20-80 years. In 136 cases a hypertonia was found (blood pressure over 140 mm Hg), 29.4 per cent. In 65 of these 136 diabetics ketonuria was present, 47.7 per cent. A similar study made of 1800 non-diabetics in the same age-limit, 20-80 years (1055 males, 745 females), showed a high blood pressure (over 140 mm Hg) in 616 cases, that is in 34.3 per cent. A comparison as to the incidence of hypertonia in diabetics and non-diabetics, showed it to be present in 29.4 per cent of the former as compared to 34.3 per cent in the latter, thus the number of cases of hypertonia among diabetics was 49 per cent less than among non-diabetics. The occurrence of low blood pressures among diabetics was first shown by Hitzenger, who found that the blood pressure in young diabetics was considerably lower in a greater percentage than in non-diabetics of the same age. As the cause of the low blood pressure he assumed that it was dependent upon the

accompanying acidosis, since the blood pressure rose when this was lessened or disappeared. Joslin also states that the blood pressure in diabetics under 25 years is usually below normal. Barach noted in these cases of diabetes in which the pressure was low that there was a marked emaciation or general body weakness. Wiechmann found a hypotonia in 26 per cent of male diabetics under 30 years of age, and according to the statistics of J. Barach 37 per cent of diabetics have a low blood pressure (under 110 mm Hg). Kisch found in his 463 diabetics 58 cases in which the arterial blood pressure was 100 mm Hg and lower, that is, in 12.5 per cent. In 30 of these 58 cases with arterial hypotonia there was a concomitant ketonuria. In the 1800 non-diabetics (1055 males, 745 females) there were 265 with a low arterial pressure, that is, 14.7 per cent. Comparison of the number of hypotonic cases in diabetes with the number in non-diabetic cases, there were 12.5 per cent of the former in contrast to 14.7 per cent in the second group. Comparing the blood pressure curves with the blood sugar curves he found that neither in diabetics or in non-diabetics, be the blood pressure high or normal, was there any increase in blood pressure at the time of the greatest height in blood sugar. He, therefore, concludes that hyperglycemia as such is without influence upon the blood pressure, that with the highest, medium and moderate degrees of hyperglycemia, the percentage of diabetics with normal blood pressure remains about the same. Neither in diabetics or in non-diabetics is there any conformity between the blood pressure and blood sugar curves. In 16-19 per cent of cases of completely de-sugared diabetics a lowering of blood pressure occurs at the time of complete aglycemia, probably as the result of the fasting condition. Insulin treatment is therefore, without significance in its effect upon the blood pressure. As far as ketonuria is concerned in the question of high or low blood pressure 47.7 per cent of the diabetics with arterial hypertension and 51.7 per cent of diabetics with arterial hypotension showed ketonuria, a practically equal relationship showing that there is no essential relationship between ketonuria and the conditions of blood pressure.

## Reviews

*Tumors Arising from the Blood Vessels of the Brain Angiomatous Malformations and Hemangioblastomas* By Harvey Cushing, Professor of Surgery, Harvard Medical School and Surgeon-in-Chief, The Peter Bent Brigham Hospital, Boston, and Percival Bailey, Formerly Associate in Surgery, The Peter Bent Brigham Hospital and Associate Professor of Surgery, University of Chicago 219 pages, 150 illustrations Charles C Thomas, Springfield, Illinois and Baltimore, Maryland, 1928 Price in cloth \$7 50

This is a clinicopathological study in which experimentation plays no part. The pathological specimens on which it is based have been in process of collection over a period of nearly twenty-five years. It was begun at the Johns Hopkins Hospital and has been continued at the Peter Bent Brigham Hospital. Although in Cushing's experience the hemangiomas of the brain are in proportion to other intracranial tumors as only two to one hundred, the clearing up of some of the obscurities of a minor group of tumors may sometimes indirectly throw unexpected light on the whole. The book treats in Part I of the angiomatous malformations, angioma venosum and angioma arteriale, which together are illustrated by fourteen cases. There follows the case reports a general discussion of the symptomatology, pathology and treatment of the various forms. Part II treats of the cerebellar hemangioblastomas, illustrating them by eleven cases, with a discussion of symptomatology, pathology and treatment. This is followed by a short discussion of cerebral hemangioblastomas. This is an interesting little monograph based upon a relatively small number of cases, studied in connection with the literature. It will make an especial appeal to the pathologist and brain surgeon. A specially valuable feature of

the case reports are the controlled records of the cases. The book is excellently printed, and the illustrations unusually good. The bibliography is also a valuable feature of the book.

*Racial Hygiene A Practical Discussion of Eugenics and Race Culture* By Thurman B. Rice, A.M., M.D., Associate Professor of Bacteriology and Public Health, Indiana University School of Medicine, Extension Lecturer in Eugenics, Indiana University, Chairman Indiana Eugenics Committee 376 pages, 58 figures. The MacMillan Company, New York, 1929. Price in cloth \$4 50.

The plan of this book is to present the fundamentals of genetics, the science of heredity in the earlier chapters, in order that the biological foundation may be laid for the sociologic application to be made in the succeeding chapters. The importance of the biologic basis for eugenics and for the understanding of sociology, of social work, of educational systems, of disease, delinquency, degeneracy, crime, pauperism and mental defectiveness is being more and more appreciated. Much effort has been put forth to make the biologic basis accurate according to the latest scientific verdict. For the most part subjects still in controversy are avoided or handled in the manner that seems most likely to avoid unnecessary confusion. It is not intended that the opinions expressed in regard to various social problems shall be regarded as final since there is room for wide divergence of opinion on all such matters, but the author insists that the basis of a great number of perplexing social problems is biological. If the cause of an anti-social condition is found in a biologic relation, then it seems reasonable that the logical remedy is the correction of the cause, if this is possible. It seems absurd to attempt to correct such a condition with education, religion, philanthropy, psychology or any other

of the thousand and one remedies which have been recommended. The author believes that eugenics constitutes a biologic problem with sociologic implications. The reader is reminded that the welfare of the race rather than that of the individual is the aim of this book, but that the welfare of the race will ultimately mean the greatest good to the greatest number of individuals. The author hopes that the matter presented will be found interesting as well as instructive, and that it may not be adjudged impractical ultimately because it cannot be applied immediately. It may be generations before an adequate program can be evolved. But even so it is better that eugenics grow into its proper place slowly rather than prematurely. The education of thinking people in the principles of race culture and hygiene is the first and most important step in the preparation of the soil. The book presents the basic facts of genetics and eugenics in simple and understandable language, which may be easily understood by any intelligent reader. The laws of heredity are made clear to the layman. It is the most practical book on eugenics that has yet been written, and as such may be warmly recommended to all readers. It cannot fail to accomplish a most useful end in making intelligible to the layman the laws of heredity and reproduction.

*Gould's New Medical Dictionary, Containing All the Words and Phrases Generally Used in Medicine and the Allied Sciences, With Their Proper Pronunciation, Derivation and Definition. Based on Recent Medical Literature. By George M. Gould, A.M., M.D., Edited by R. J. E. Scott, M.A., B.C.L., M.D., Fellow of the New York Academy of Medicine. Second Edition. Revised and Enlarged. 1522 pages, with numerous illustrations and 170 tables, including a new one of micro-organisms, comprising 68 pages, by D. H. Bergey, M.D., Professor of Hygiene and Bacteriology, University of Pennsylvania. P. Blakiston's Son and Company, Philadelphia, 1929. Price in cloth \$7.00, with thumb index \$7.50.*

The first of Dr. George M. Gould's medical dictionaries was published in 1890, under

the title of "A New Medical Dictionary." Two years later "A Pocket Medical Dictionary" of 12,000 words was published, and this was followed, in 1894, by his monumental work "An Illustrated Dictionary of Medicine, Biology and Allied Sciences" the current edition (6th) of which comprises 1700 double columned pages. Ten years later, a supplement to the Illustrated Dictionary, containing 38,000 words was published under the title of "A Dictionary of New Medical Terms." The title of the first dictionary, namely, "A New Medical Dictionary" was in a later revision changed to "The Student's Medical Dictionary" which contained a much larger vocabulary. Under this title the book was continued with revisions until 1906, when it gave place to a new and larger issue entitled "The Practitioner's Medical Dictionary" which has served the profession for a number of years, and may still continue to do so. We come now to the present issue "Gould's Medical Dictionary", which may be said to be the sum of all of Gould's dictionaries. The important features of this new and latest dictionary are the larger and bolder type, the additional pictures, the increase in size of the volume, the added biographical detail, and many new abbreviations now employed in current medical literature. It contains about 76,000 words, hundreds of which are new terms. Other new features are a physician's and a veterinary dose table, based on the U. S. P., X, a diet table and a table of micro-organisms by Dr. D. H. Bergey. The interests and needs of the busy practitioner and the active general medical reader have been kept in mind. No matter has been inserted that is not appropriate, and few pictures are included that are in the most commonly used text and reference books. Eponymic terms are in their proper alphabetical order, so that one no longer need be in doubt whether to look under test, reaction, phenomenon, syndrome, sign or symptoms, etc., for the information sought. The tabulation and systematic classification of other correlated terms established in usefulness, have been continued. The spelling conforms to the standard requirements, and the definitions are based

upon the standard literature and authoritative textbooks of the day, and are not copies from the older vocabularies. The pronunciation is clearly shown by a phonetic arrangement of letters. The original alphabetical sound of the letter is the key. Only when there may be any doubt has the pronunciation been indicated by a diacritic mark. Proper names and their derivations only have been capitalized in the titlewords, in accord with present usage. The constant aim of the publisher and editor has been to make this new dictionary more accurate, more comprehensive and more helpful. Over 706,000 volumes of Gould's Medical Dictionaries have been distributed over the world, a fact that attests their intrinsic value. This dictionary will be found most practical and serviceable. It shows a high standard of accuracy, and is brought up to date as fully as any dictionary may hope to be. In checking over the newer terms the reviewer notices the absence of "blastophthoria," "cyclostage," and a number of the most recent terms used in modern bacteriology. Just why "blastophthoria" should have escaped the editor it is difficult to see, for this term is one of the most commonly used in the medical genetics of the present time. The definition of "disassociation" makes no reference to its usage in bacteriology. "Dysontogenesis" is another important common term of pathology which is wanting, as is also the bacteriologic term "tropin," and the genetic term "linkage." The deficiencies of this dictionary are most prominent in the terminology of modern pathology, bacteriology and genetics. Nevertheless it is a most useful and valuable book, especially fitted for the needs of the medical student and practitioner. The definitions are for the chief part excellent and terse. It is the best of all the medical dictionaries published in the English language, and for this reason it is highly recommended.

Eden Paul, M D, Brux, M R C S, F R C P. New Second Edition. Volume I, Containing Sections on Regions of Human Body—Osteology—Arthrology—Myology (Figures 1-640 and General Index). Volume II, Containing Sections on Splanchnology—Angiology—Neurology—Organs of the Senses (Figures 641-1505, with Appendices and General Index to the two volumes). The MacMillan Company, New York, 1928. Price in cloth, \$20.00.

This new second edition of the Toldt Atlas of Human Anatomy has been revised and corrected, and in its present form constitutes the most complete and best of the various atlases on human anatomy that has yet been offered. The illustrations are excellent, and are especially noteworthy for their accuracy and simplicity. There is no descriptive text, but the figures present so well what they are intended to do, and the parts are so well labelled, that the book reveals the various anatomical structures and their relationships as clearly as in an actual dissection of the given part. Both the American and International terminologies are given. The two volumes are an invaluable aid to the medical student of anatomy, and should be in the hands of every one during his dissection of the human subject. Further, for the purpose of a quick refreshing of one's anatomical memory this atlas is most serviceable. It can be highly recommended to both the medical student and the surgical practitioner.

*The Blood Plasma in Health and Disease*  
By J. W. Pickering, D Sc (Lond), Lecturer on Hematology, University of London, King's College. Monographs of Medical and Surgical Science, Edited by R. J. S. McDonald, D Sc, M D, F R C P (Edin), University of London, King's College. 247 pages. The MacMillan Company, New York, 1928. Price in cloth \$1.25.

value not only to the research worker, but, by the avoidance of undue technical detail in the applied chapters, that they should also be of practical use to the clinician. Blood plasma has been investigated from the standpoint of bio-chemistry, physiology and pathology. Each of these branches of research has revealed important truths, but the differences of outlook among workers have often led to the treatment of this subject in compartments. An attempt will be made in the limits of this small volume to correlate certain facts derived from each of these sources of information, and to point out some of their practical applications. Evidence will be collated which suggests that the plasma is of fundamental importance in the life of the whole body, and it will be shown that morbid conditions appear when the stability of plasma is altered. Modern knowledge of the plasma is largely derived from the investigation of the precipitability and coagulability of that fluid. Following a historical introduction, the various chapters treat in succession of the protein of blood plasma in

fractions and as a whole, fibrinogen, the inception of blood clotting, the stabilization of blood plasma, thrombosis and anti-thrombosis, fibrin, the suppression of the coagulability of the blood in vivo, the condition of the blood in anaphylactic and anaphylactoid states, current theories of blood coagulation, the arrest of hemorrhage, the problem of thrombosis, menstrual and puerperal blood, and the blood of abnormal bleeders. Following these are three appendices on Synapsis of the newer hemostatics, general bibliography and the bibliography of methods of extracting fibrin. This volume sums up what is known of the blood plasma in health and disease. Particularly important is the critical discussion of our present knowledge on coagulation of the blood and thrombosis, and on congenital hemophilia. It is an important book for the medical student, laboratory worker and for the practitioner as well. It contains much information of practical value to the practising physician in its discussion of bleeding and its treatment.



JOHN H. MESSERT M.D.,  
President, American College of Physicians, 1929-30  
(1551 Canal Street New Orleans, La.)

## College News Notes

During the Thirteenth Annual Clinical Session of the American College of Physicians at Boston, April 8-12, Dr John Herr Musser was inducted as President of the American College of Physicians for the succeeding year, having been elected President-Elect at the Twelfth Annual Clinical Session at New Orleans in March, 1928

Dr Musser was born in Philadelphia, June 9, 1883, received his Baccalaureate Degree at the University of Pennsylvania in 1905 and his Medical Degree at the same institution in 1908. He is the sixth Musser physician in direct descent from the original one who came over to this country in the early part of the eighteenth century. He was Assistant Physician to the Presbyterian Hospital, Philadelphia, 1912-24, Physician to the Philadelphia General Hospital, 1914-24, Physician to the Howard Hospital, Philadelphia, 1919-24, and Assistant Professor of Medicine at the University of Pennsylvania Medical School, 1919-24. From 1911 to 1920, he was Assistant Editor of the American Journal of Medical Sciences, and from 1920 to 1924, Editor of the same Journal, which is the oldest medical journal in the United States. Dr Musser terminated his Philadelphia appointments in 1924 to become Professor of Medicine at Tulane University of Louisiana, School of Medicine, New Orleans, which appointment he still holds. He is Physician to the New Orleans Charity Hospital and Editor of the New Orleans Medical and Surgical Journal. During the World War, he was successively commissioned Lieutenant, Captain and Major, in charge of the Medical Service of the University of Pennsylvania Base Hospital, No 20, A E F. He is now Lieutenant-Colonel in the Medical Reserve Corps.

Dr Musser is a member of the Psi Upsilon and the Alpha Mu Pi Omega fraternities. He is a member of the Orleans

Parish Medical Society, the Louisiana State Medical Society, a Fellow of the American Medical Association, member of the American Climatological and Clinical Association, member of the Society for Experimental Biology and Medicine, member of the American Society for Clinical Investigation, member of the Association of American Physicians, member of the Southern Medical Association, and has been a Fellow of the American College of Physicians since June 20, 1920. He has served on various important committees, and has been a member of the Board of Regents of the College for several years. As General Chairman of the New Orleans Clinical Session of the College in 1928, he distinguished himself as an organizer of unusual ability, and displayed those qualities which contribute greatly to co-operation, efficiency, high standards and cordiality.

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Dr Grafton Tyler Brown (Fellow), Washington, D C, has been reappointed Chairman of the Membership Committee of the Medical Society of the District of Columbia.

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Dr Robert M Moore (Fellow), Indianapolis, Indiana, addressed the Summit County Medical Society at Akron, Ohio, February 5. His subject was "Some Considerations in Heart Failure of the Anginal Type."

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Dr E J G Beardsley (Fellow), Philadelphia, Pa, addressed a Postgraduate audience in the historic Clinical Amphitheatre of the University of Maryland, Baltimore, on January 31, his subject being "Emphysema and its Complications."

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Dr Alfred W Gray (Fellow), Dr C H Stoddard (Fellow) and Dr R W Blumenthal (Fellow) are all members of



the Board of Directors of the Medical Society of Milwaukee County, Milwaukee, Wisconsin

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Dr F C Potter (Fellow), Akron, Ohio, is President of the Summitt County (Ohio) Medical Society for 1929, and Chairman of the Medical Committee of the Red Cross Disaster Relief, Summitt County Chapter

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Dr William C Voorsanger (Fellow), San Francisco, is Medical Director of The Oaks Sanitarium, Los Gatos The Oaks Sanitarium celebrated its fifteenth birthday during the week, February 15-22 This is an institution for the treatment of Tuberculosis and allied pulmonary conditions

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Dr Harry M Hall (Fellow), Wheeling, West Virginia, published an article entitled "Relation of the Hospital Staff to the Directorate and Superintendent" in the February Issue of the West Virginia Medical Journal and also in the February Issue of Hospital Management Dr Hall is President of the West Virginia State Medical Association

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Dr Lee Rice (Fellow), San Antonio, Texas, is a Governor for Texas of the Gorgas Memorial At the last meeting of the Southern Medical Association in Asheville, he was elected Chairman of the Medical Section Under the direction of the Gorgas Memorial Institute, which is organized to perpetuate the life work of the late Major-General Gorgas in preventing unnecessary illness, Dr Lee Rice has contributed a number of articles, which have had wide circulation Among these are "Heart Disease" and "Preparation for Inevitable Heart Disease Made by Combination of Infection and Overstrain"

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Dr Louise Tayler-Jones (Fellow), Washington D C, attended the Medical Women's National Association meeting at Paris April 11-13

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In the January Issue of the Southern Medical Journal, the following articles were contributed by Fellows of the College

"The Promotion of the Common Welfare The Aim of Modern Medicine," by William R Bathurst, Little Rock, Ark

"Is Malignant Hypertension a Disease Entity?" by J B McElroy, Memphis, Tenn

"Relation of Medical Education to the Public," by Stuart Graves, University, Ala

"A Decade of Transition in American Psychiatry," by W E Gardner, Louisville, Ky

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The following Fellows appeared on the Program of the 45th Annual Convention of the Tri-States Medical Association of Mississippi, Arkansas and Tennessee at Memphis, February 6-8

Dr. R H Balyeat, Oklahoma City

Dr Frank Smithies, Chicago

Dr L G Rowntree, Rochester, Minn

Dr John H Musser, New Orleans

Dr Lawrason Brown, Saranac Lake

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Dr C Lydon Harrell (Associate), Norfolk, Virginia, addressed the Warwick County Medical Society, January 28, on "Calcium Deficiency in Disease"

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Dr Sinclair Luton (Fellow), St Louis, Missouri, was a guest of the Jackson County (Illinois) Medical Society at its annual meeting in Carbondale, Illinois, December 20, 1928 Dr Luton addressed the meeting on "Diseases of the Heart"

Dr Luton addressed the Frisco System Medical Association's annual meeting at Pensacola, Fla, October 22-23, 1928, on "The Diagnosis of Chronic Heart Disease"

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Dr Linn J Boyd (Fellow), New York, N Y, is author of an article in the January Issue of the Journal of the American Institute of Homeopathy, entitled "The Necessity for a Scientific Concept of Homeopathy"

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Dr Carl V Vischer (Fellow), Philadelphia Pa, Associate of Devitt's Camp for the treatment of Pulmonary Tuberculosis, is author of an article in the January number of the Journal of the American Institute of Homeopathy, entitled "Ultra Violet

Rav in the treatment of Pulmonary Tuberculosis," with case reports

Dr James M Anders (Master), Philadelphia, Pa, addressed the association of College Presidents of Pennsylvania on the "Research Method of Teaching Science," November 24, 1928, at Harrisburg

Dr Donald R Ferguson (Fellow), Philadelphia, Pa, was recently elected Chairman of the Bureau of Clinical Medicine of the American Institute of Homeopathy

Dr Linn J Boyd (Fellow), New York, N Y, sailed for Europe on December 22 for a series of personal conferences with the Homeopathic Leaders of England, Belgium, Holland, Germany, Italy, Spain, Switzerland and France, in preparation for the European reception of the 1929 International Committee of the American Institute of Homeopathy which will sail for Europe on June 27, 1929

Dr Linn J Boyd (Fellow), of the New York Homeopathic Medical College has been conducting extensive "Drug Proving" experiments with the aid of a "Proving Squad" consisting of medical students of the College Dr Boyd is also Chairman of the Bureau of Drug Pathogenesis of the American Institute of Homeopathy

Dr Carl V Vischer (Fellow), Philadelphia, Pa, is author of another article on the Treatment of Tuberculosis which appeared in the January number of the Hahnemannian Monthly entitled "Management of the Chronic Tuberculous Patient"

Dr Albert D Foster (Fellow), formerly stationed at the U S Marine Hospital at Boston, Chelsea, Massachusetts, where he is Medical Officer in Charge

Dr Lester L Powell (Associate), Portland, Maine, has been elected President of the Portland Medical Club for the year 1929 Dr Eugene H Drake (Associate) was the retiring president

Dr William Thalheimer (Fellow), formerly Director of the Laboratory of Pathology of Columbia Hospital, Milwaukee, Wisconsin, accepted on February 1 the appointment of Director of Laboratories of the Michael Reese Hospital, of Chicago Dr Thalheimer's new address is The Nelson Morris Institute, 29th and Ellis Avenues, Chicago, Illinois

Dr Thomas J Burrage (Associate) was appointed Chairman and administrative head of the emergency staff organized in Portland, Maine, for relief against influenza or an epidemic of any other nature, recently organized by the Portland Chapter of the American Red Cross Dr Lester L Powell (Associate) was appointed Director of the Immanuel Baptist Parish House Hospital, with a capacity of more than 250 cots, in connection with the same organization

Dr George G Hunter (Associate), Los Angeles, Calif, has been elected President of the Los Angeles County Medical Association for 1929, and Secretary-Treasurer of the Los Angeles Clinical and Pathological Society

The following appointments on the faculty of the University of Oregon Medical School were published recently in *Northwest Medicine*

Dr Noble W Jones, Clinical Professor of Medicine

Dr T Homer Coffen, Clinical Professor of Medicine

Dr Harold C Bean, Assistant Clinical Professor of Medicine

Dr Ralph C Matson, Associate Clinical Professor of Medicine

Dr James Marr Bisailon, Assistant Clinical Professor of Medicine

Dr Isidor C Brill, Assistant Clinical Professor of Medicine

Dr Charles E Sears, Assistant Clinical Professor of Medicine

Dr George H Hovik (Fellow), Kansas City, Missouri, was recently appointed a member of the Jackson County Medical Society Cardiac Committee, which is to co-

operate with the Health Conservation Association of Kansas City in a program to survey facilities for the prevention of heart disease and to handle cardiac patients

Dr Frederick A Willius (Fellow) of the Mayo Clinic addressed the Omaha-Douglas County Medical Society at Omaha, Nebr, January 22, on "Digitalis in Clinical Medicine"

Dr Lester J Palmer (Fellow), Seattle, Washington, addressed the King County Medical Society, February 4, on "Simple Method of Preparation of Dextrose for Intravenous Administration"

The annual meeting of the East Mississippi Medical Society at Meridian on December 18, 1928, was addressed by the following Fellows

Dr Allan Eustis, New Orleans, "Myocardial Insufficiency"

Dr James S McLester, Birmingham, "Constipation"

Dr Charles Holbrook (Fellow), New Orleans, Louisiana, spoke on "Newer Methods of Treating Syphilis of the Nervous System" before the South Mississippi Medical Society at Laurel, December 13, 1928

Dr Herman Trossbach (Fellow), Bogota, New Jersey, has been appointed Director of the Medical Service of the Hackensack Hospital

Dr Clyde L Cummer (Fellow), Cleveland Ohio, was recently elected Chairman of the Board of Trustees of the Cleveland Medical Library Association

Dr Charles W Stone (Fellow), Cleveland, Ohio, addressed the Sandusky County Medical Society recently on "Psychologic Healing in Antiquity"

Dr John D Dunham (Fellow) Columbus Ohio, addressed the Columbian County Medical Society, December 4 1928, on "Methods and Evaluation of Physical Examination"

Dr Samuel E Munson (Fellow), Springfield, Illinois, addressed the Adams County Medical Society, February 11, on "Hypertension"

The following appointments of Department Heads for 1929 and 1930 at the City Hospital, Cleveland, have been recently announced by the Dean of the Western Reserve University School of Medicine

Dr Charles W Stone (Fellow), Neuropsychiatry

Dr Howard T Karsner (Fellow), Pathology

Dr Joseph C Placak (Fellow), Tuberculosis

Dr Edward L Tuohy (Fellow), Duluth, Minnesota, addressed the Minnesota Academy of Medicine, February 13, at Saint Paul

Dr Charles H Neilson (Fellow), St Louis, Missouri, presented a paper on "Preparation of the Patient for Operation from the Standpoint of the Internist" before the Randolph-Monroe County Medical Society, December 20, 1928

Dr John H Musser (Fellow), New Orleans, Louisiana, addressed the Nashville Academy of Medicine (Tennessee), February 5, on "Throat Infections in General Medicine"

Dr Thomas Hall Shastid (Fellow) is author of an article "My Father Knew Lincoln" in the Nation for February 20, 1929. In this article there occurs an interesting explanation of a peculiarity of Lincoln's physiognomy that has never been previously noted. "There was one point that my father had noted about Lincoln's physiognomy that I have never seen recorded. It was that the left eye, from time to time, looked queer and then suddenly 'crossed,' i.e., turned up. At the time when my father told me this it did not strike me as having the least importance. Older grown, however, and become an oculist, I was struck one day by the recollection and then by the meaning of the fact itself. Lincoln had

been the victim of hyperphoria (a *tendency* of one eye upward) with, now and then, a momentary hypertropia (actual *turning* of one eye upward) Such a condition, as all oculists know, gives rise to an intense form of eyestrain and is one of the commonest causes of deep and protracted melancholy—the chronic, inexpressible blues Here, then, was the probable explanation of the well-known Lincolnian depression of spirits which lasted, off and on, until his death"

#### DR WARTHIN TO BE HENRY RUSSEL LECTURER

This year the appointment as Henry Russel Lecturer of Dr Aldred Scott Warthin, Michigan's distinguished Professor of Pathology, has been announced The roll of honor of previous Henry Russel Lecturers consists of Professor Moses Gomberg, in 1926, Professor Frederick G Novy, in 1927, and Professor Henry Arthur Sanders, in 1928 The Henry Russel Award has gone in past years to Assistant (now Associate) Professor Carter Goodrich of the Department of Economics, in 1926, Assistant Professor Albert Hyma of the Department of History, in 1927, and Assistant Professor Laurence M Gould of the Department of Geology, now with the Byrd Antarctic Expedition, in 1928 The winner of the Award for 1929 will be announced at the time of the Lecture, in May Michigan, too, has its own "Nobel Prizes" in the Henry Russel Lectureship and the Henry Russel Award, derived from the endowment fund bequeathed to the University by the late Mr Henry Russel of Detroit

#### BRIEF REPORT OF THE BOSTON CLINICAL SESSION

The Thirteenth Annual Clinical Session of the American College of Physicians was held at Boston, April 8-12, 1929 The meeting has been acclaimed as the largest and one of the most successful sessions that the College has ever conducted There were 1,464 official registrations, physicians being present from every State in the United

States, with the exception of Nevada There were, in addition, attendants from various Provinces of Canada, from Panama, Colombia (South America), England, Italy, Denmark and China

The program was divided between clinics in the various Boston hospitals each morning, and general sessions in the afternoon and evening in the Assembly Hall of the Hotel Statler

The clinics were reported to be of unusual merit with interest, particularly because patients were shown generally The general sessions, during the afternoons and evenings, were diversified in content and participated in by the leading authorities of the country

The commercial exhibits were of more than average merit and were splendidly arranged in the foyer of the general assembly hall, where attendants at the session could conveniently examine new publications, pharmaceutical products and apparatus, when coming and going from the general meetings The effort was to secure, not a large number of exhibitors, but a selected group whose products would be of especial interest to the members of the College

One hundred and ninety three new members were elected to Fellowship by the Board of Regents and about two hundred and fifty inducted at the Convocation on Friday evening, April 12 Fifty-four physicians were elected to the Associate group

A special feature was the conferring of five Masterships on Fellows of the College in recognition of their positions of influence and honor an eminence in practice, or of medical research and distinguished service to the College Those to whom Masterships were conferred were Alfred Stengel, Philadelphia, Pa, Charles F Martin, Montreal, Que, Charles G Jennings, Detroit, Mich, Aldred Scott Warthin, Ann Arbor, Mich, Frank Smithies, Chicago, Ill

The names of those elected to Fellowship and to Associateship will be published in a later number

The new Officers of the College for 1929-30 are President, John H Musser New Orleans, La, President Elect, Sidney R Miller, Baltimore, Md 1st Vice President

Aldred Scott Warthm, Ann Arbor, Mich , 2nd Vice President, F M Pottenger, Monrovia, Calif , 3rd Vice President, Logan Clendenning, Kansas City, Mo , Treasurer, Clement R Jones, Pittsburgh, Pa , Secretary General, George Morris Piersol, Philadelphia, Pa , Executive Secretary, E R Loveland, Philadelphia, Pa

New members of the Board of Regents, elected for three years are David P Barr, St Louis, Mo , Arthur R Elliott, Chicago, Ill , Noble Wiley Jones, Portland, Ore , Maurice C Pincoffs, Baltimore, Md , S Marx White, Minneapolis, Minn

New members of the Board of Governors,

not heretofore members of that Board, elected for a period of three years, included the following William Gerry Morgan, Washington, D C , Roger I Lee, Boston, Mass , Edward B McCready, Pittsburgh, Pa , J O Manier, Nashville, Tenn , Charles Edward Riggs, U S Navy , Hugh Cumming, U S Public Health Service, Harvey Beck, Baltimore, Md , A Comingo Griffith, Kansas City, Mo , C H Cocke, Asheville, N C , E J G Beardsley, Philadelphia, Pa , James G Carr, Chicago, Ill , Harlow Brooks, New York, N Y , Hans Lisser, San Francisco, Calif , C H Beecher, Burlington, Vt

# A Note on the Composition of Human Sweat\*†

RALPH PEMBERTON, M.D., F. A. CAJORI, Ph.D. and C. Y. CROUTER, M.S.,  
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INCREASING attention is being devoted to the general field of physiotherapy in the treatment of disease. One of the oldest and most valuable measures in this field is exposure of a part or all of the body to external heat. A conspicuous consequence of this form of treatment is the sweating which is induced. This is so striking a phenomenon as to have led in many quarters to the supposition that toxic material of various kinds may be eliminated in this way. In view of the importance of the sweating process as a therapeutic measure and in view of the relative paucity of precise data bearing upon it, it becomes important to ascertain, if possible, what actually occurs.

For a number of years the physiological effect of external heat, therapeutically applied, has been the subject of investigation in this laboratory. During the course of these studies, considerable data has accumulated relative to the composition of human sweat. The chemistry of sweat in

health and diseased conditions, particularly in various skin disorders, has attracted the attention recently of a number of investigators and it seems desirable to make available our existing data, fragmentary though some of it is. This conclusion is further strengthened by the improbability that the present experiments can be carried to completion in the near future by the present workers. These data, which have not been published before have to do, in part, with the reaction of sweat under various conditions and from various parts of the body and with an endeavor to ascertain the factors involved in its reaction. Some figures are available relative to the reaction and to the nitrogen and chloride content of sweat in arthritis, nephritis, scleroderma and psoriasis.

## REACTION OF SWEAT

Sweat as collected may be either acid or alkaline, the range of reaction being about the range which has been observed for urine, namely, pH 4.8 to 8.4. As has been pointed out before by Pemberton and Crouter (1), the initial sweat is usually more acid than that which is secreted later, if conditions favorable for sweating are maintained. This change in reaction seems to be a compensatory measure to the systemic alkalosis which de-

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†The work here reported is part of a study on chronic arthritis in collaboration with R. B. Osgood, M.D., of Boston. The expenses were defrayed by contributions from various sources, including a number of patients.

velops during a "bake," hot bath or other systemic exposure of the body to external heat (2)

It is questionable whether the true reaction of sweat as it is secreted can be measured in samples collected from the surface of the skin. Upon secretion, sweat is exposed to the air and possible loss of  $\text{CO}_2$  and other volatile constituents, which may, in part, determine its reaction, may occur. It is well known that  $\text{CO}_2$  is given off from the skin in appreciable amounts during sweating. The reaction of sweat and its  $\text{CO}_2$  content has been investigated to some extent by Kittsteiner (3) and Talbert (4).

In order to evaluate the rôle of  $\text{CO}_2$  in the reaction of sweat, the total  $\text{CO}_2$  content has been determined in sweat samples, and the effect on the reaction of the removal of  $\text{CO}_2$  by aeration and boiling has been studied. For this purpose, sweat was collected in a rubber bag that fitted over the hand and forearm of the subject. With the aid of adhesive plaster the bag was tightly sealed around the arm above

the elbow. The bag was provided with an outlet tube and the sweat when collected, was allowed to flow through this tube, under oil, into a receptacle. The arm and hand were cleaned with alcohol and ether before being inserted into the bag. The sweat so collected will be referred to as "bag sweat." Sweat from other parts of the body was taken up from cleansed areas in blood-counting pipettes. The pH of the sweat was determined by Felton's spot method (5). This method was of advantage in this work in that it could be carried out on very small amounts of material. It can not be claimed that results obtained in this way are highly accurate ( $\pm 0.1$  pH unit), but in the case of sweat, the results of more accurate analytical determinations would probably be of little significance for the reasons already mentioned. Total  $\text{CO}_2$  was determined in the Van Slyke apparatus.

The total  $\text{CO}_2$  content of sweat was found to be very low, even in the more alkaline sweats and, as will be seen from the results in Table I, rarely ex-

TABLE I  
Total  $\text{CO}_2$  Content of "Bag" Sweat

No	pH	$\text{CO}_2$ vols per cent		No	pH	$\text{CO}_2$ vols per cent		No	pH	$\text{CO}_2$ vols per cent
1	4.8	0.9		15	6.2	1.9		43	7.0	2.3
6	4.8	0.5		26	6.4	0.9		34	7.0	3.0
8	5.2	0.8		39	6.4	0.2		35	7.2	4.1
10	5.3	3.6		41	6.4	0.6		37	7.2	1.8
10	5.6	0.2		11	6.4	0.8		45	7.2	1.5
11	5.8	3.7		23	6.6	1.1		46	7.2	2.8
22	6.1	0.7		24	6.6	2.5		42	7.1	4.7
14	6.2	2.3		33	7.0	5.6				

ceeds 4 volumes per cent. The more acid sweats (pH 4.8 to 6.4) in general contain much less  $\text{CO}_2$  than those whose pH is higher. Since many sweats contain mere traces of  $\text{CO}_2$ , the reaction of sweat would seem frequently to be due to constituents other than carbonic acid or bicarbonates. Carbon dioxide may, however, influence a sweat reaction as is clearly shown by the change in pH that follows the removal of  $\text{CO}_2$  from an alkaline sweat of comparatively high  $\text{CO}_2$  content. Also, sweat collected in a rubber bag surrounding the arm and therein exposed to a  $\text{CO}_2$  tension of the order of 3 to 8 mm of mercury, was more acid than sweat collected simultaneously from the other arm (Table III).

The effect on the reaction of bag sweat of driving off the  $\text{CO}_2$  which it contained was investigated. Sweat samples were boiled half a minute or aerated for half an hour with a rapid stream of air. The effect on the pH of allowing sweat to stand several hours was also studied. The results of these observations are given in Table II. Very little change in pH was observed in those sweats with an initial acid reaction after the removal of  $\text{CO}_2$ . Other sweat samples, with a higher pH and presumably a higher  $\text{CO}_2$  content, became decidedly more alkaline after boiling and aeration. Exposure to room air had little or no effect on the reaction of the sweat. In our series it was not infrequently observed that after boiling, a sweat

TABLE II

Effect of Boiling, Aeration and Contact with Air on the pH of "Bag" Sweat

No	Initial pH	After Boiling pH	After Aeration pH	After Contact with air pH	No	Initial pH	After Boiling pH	After Aeration pH	After Contact with air pH
1	4.8	4.8	4.8	4.8	39	6.4	6.4	6.4	—
3	4.8	4.8	4.8	—	41	6.4	6.4	6.4	—
6	4.8	4.8	4.8	—	20	6.6	6.6	7.1	6.6
4	5.0	5.0	—	—	21	6.6	6.4	7.0	—
7	5.2	5.0	5.0	5.0	25	6.8	7.0	—	6.8
8	5.2	5.2	5.2	—	26	6.8	6.6	7.0	6.9
9	5.6	5.8	5.8	—	28	7.0	7.2	—	7.0
10	5.6	5.6	5.6	5.6	29	7.0	7.4	—	7.0
12	6.0	6.0	—	6.0	30	7.0	7.0	—	7.0
13	6.0	7.7	7.4	—	31	7.0	6.6	8.0	7.1
16	6.4	6.2	6.4	—	32	7.0	8.0	—	7.1
17	6.4	6.0	6.4	—	33*	7.0	8.2	—	—
18	6.4	6.4	—	6.4	36	7.2	8.0	7.8	—
19	6.4	6.3	—	6.4	37	7.2	7.2	—	—
38	6.4	6.4	6.4	6.4					

\*Initial  $\text{CO}_2$  content, 5.6 vols per cent. After boiling 0.8 vols per cent.



sample was slightly more acid than it was before it was boiled Kittsteiner observed the same phenomenon when he boiled sweat This increase in acidity was not observed during aeration and consequently it would seem to result from the formation, during heating, of some product acid in nature, rather than to the loss of a volatile base

Since acid sweat contains only very small amounts of  $\text{CO}_2$ , the alkaline swing observed during sweating is probably the result of an increased elimination in the sweat of basic substances This bears out the conclusion that the alkalosis observed during the exposure to heat is caused by loss of  $\text{CO}_2$  by the body, which is partly compensated by excretion of base (2). Analysis of sweat for total base at intervals during sweating does not always reveal this relation however, for

the analytical results must be expressed in per cent composition, and it has been shown that a dilution of sweat occurs during continued sweating (6) This dilution factor may mask the actual increase of base being excreted In Table III are a few results on total base determinations in sweat, made by Fisk's method (7) No correlation can be seen between the pH and the *per cent* of total base present

In Table III are also given a few determinations of the fat and fatty acid content of sweat from cleansed areas It had been noted that certain persons whose skin was distinctly greasy in appearance and feel yielded an acid sweat (forehead sweat pH 4.8) This obviously suggested that fatty acids might be the cause of the low pH Accordingly some fatty acid determinations were carried out on sweat Bloor's nephelometric method

TABLE III  
Fat and Fatty Acid Content of Sweat and Total Bases in Sweat

No	pH	Fat + Fatty Acids mgs per 100 cc		No	Initial sweat sample		Sweat sample later	
					pH	Total Bases mgs per 100 cc	pH	Total Bases mgs per 100 cc
1	5.4	103		1	5.6	64	—	—
2	5.6	14		2	5.8	82	6.2	70
3	5.6	66		3	6.0	82	6.8	50
4	5.8	216		4	6.2	50	7.0	75
5	6.4	184		5	6.6	39	—	—
6*	6.7	25		6	6.6	59	7.0	54
7	6.8	20		7**	6.6	47	7.0	60
8	6.8	83		8	6.8	68	—	—
9	7.0	26						
10	7.2	72						
11	7.4	134						

\*Scleroderma

\*\*Psoriasis

for blood was used (8), modified to meet the much smaller quantities of fatty acids present in sweat. The proportion of sweat to the alcohol-ether extraction fluid was made larger (1 to 10) than Bloor directed for blood, and weaker standards (0.4 to 2.0 mgs) were employed for the nephelometric comparisons. It was found that different sweats varied widely in their content of fatty materials. The results, which are expressed as milligrams of fatty acid per 100 cc of sweat, show no correlation between the reaction of the sweat and the quantity of total fatty acids present. There is no indication in these figures that fatty acids are concerned in the reaction of sweat.

A few observations have been made of the inorganic phosphate content of sweat, determined colorimetrically by the method of Benedict and Theis (9). Standards of suitable concentration were employed so as to match the very small quantities of phosphoric acid encountered in sweat. The inorganic phosphorus content of sweat was found to be about 0.1 to 0.3 mg per cent. There are not sufficient data from which to draw conclusions but no correlation between pH and inorganic phosphorus was suggested from the results that were obtained. The uncertainty of quantitative measurement of such small amounts of phosphorus and the unknown dilution factor of the sweat make it extremely hazardous at present to ascribe the acidity of sweat to the salts of phosphoric acid, or to any other sweat constituent that has been investigated.

Kittsteiner (4), Talbert (5) and others have noted differences in the

reaction of sweat at different sites of the body. In Table IV are recorded a few observations of the reaction of sweat secreted simultaneously from different parts of the body and taken up from cleansed areas into blood pipettes. Sweat from the forehead was found almost invariably to be more alkaline than sweat from other sites. Sweat collected from the lower part of the arm and hand was usually more alkaline than that taken from an area over the biceps muscle, though the differences in pH are small and are much less than the differences between the arm sweat and the forehead sweat. There is, however, some suggestion of an influence on the sweat from underlying muscle tissue. Very little difference in pH was found between the lower part of the arm and the lower part of the leg. A more acid sweat was usually encountered in the bag surrounding the arm. In the bag, sweat was exposed to a higher tension of  $\text{CO}_2$  than was sweat from the corresponding part of the other arm, which was free in the air.

#### SWEAT IN ARTHRITIS

The reaction, lactic acid and total organic acid content, total solids and ash of sweat in chronic arthritis have been reported previously by Cajori, Pemberton and Crouter (2) (6). In respect to these constituents no outstanding differences were detectable between the sweat of the arthritic and that of normal persons. To the above may now be added information on the total nitrogen and sodium chloride in arthritic sweat. Here again the results (Table V) are essentially the same as have been reported for normal sweat.

TABLE IV  
 PH of Sweat at different Sites on the Body

No	Fore-Head (final)	Bag	Lower part free arm	Biceps	Hand	No	Fore- head (final)	Bag	Lower part free arm	Hand	Lower part leg
9	8.2	7.0	8.2	7.4		29	8.6	7.2	8.4	8.2	
10	8.2	7.0	7.6	7.5		31	7.8	7.0	7.3	7.2	
11	8.4	6.9	7.4	7.3		32	8.4	7.4	8.0	7.6	
12	8.4	7.0	7.8	7.6		33	7.2	6.2	5.6	5.6	
13	8.2	7.0	7.4	7.1		34	8.4	7.2	7.8	7.4	
15	7.0	6.4	6.6	6.0		35	5.8	6.6	5.6	5.8	
18	7.8	6.8	7.2	6.5		37	5.4	5.8	4.8	4.9	
19	8.4	6.8	8.4	7.2		38	5.4	6.5	5.0	5.4	
22	8.2	6.6	7.1	6.8		7	7.2	6.2		7.6	
23	8.1	6.4	7.9	7.3		17	8.2	6.8		7.2	
24	8.0	7.0	7.5	7.6		30	8.2	6.6		7.2	
27	8.6	7.2	8.4	8.6		39	7.8	6.4		7.2	
20	7.8	6.2	6.8	6.5		8	7.4	6.0	6.2		
16	8.0	7.4	8.0		8.2	21	7.1	6.2	6.4		
25	8.4	7.0	7.6		7.4	36	4.8	5.3	4.6		
26	7.0	6.0	6.2		6.6	14	8.0	6.2	6.8		
28	8.0	6.6	7.8		6.6	40	6.8		5.6		5.8
						41	7.6	7.2	7.4		7.2
						42	7.0	5.4	6.0		5.8
						43	5.0	5.6	5.6		5.6

TABLE V  
 Sweat in Arthritis

Bag Sweat pH	Total N mgs per 100 cc	Bag Sweat pH	Total N mgs per 100 cc	Bag Sweat pH	NaCl mgs per 100 cc	Bag Sweat pH	NaCl mgs per 100 cc
7.0	65	5.4	102	6.6	150	6.0	220
5.6	76	—	108	4.8	150	6.8	220
6.2	77	—	131	6.0	160	6.0	230
6.8	79	7.4	165	6.4	160	6.8	250
6.4	80	6.4	197	6.8	200	6.8	330
7.2	84	5.6	232	6.8	210		
5.8	92	6.1	241	6.4	220		

The NaCl and total N agree with the results on normal sweat reported by Berry (10), Riggs (11) and Plagge-meyer and Marshall (12). The results for sweat chlorides, here reported, are below the plateau level found by Adolph (13) and the nitrogen figures are slightly higher than those recently published by Talbert, Silvers and Johnson (14).

### SWEAT IN NEPHRITIS

A few analyses of sweat collected during therapeutic "bakes" of nephritics are given in Table VI. In common with the experience of others (11), high total nitrogen was encountered in a number of the cases. It is of great clinical importance to know definitely to what extent the sweat glands in nephritis may serve as real aids in the elimination of "toxic" material. The value of sweating measures is accepted in the treatment of nephritis accompanied by edema but various workers (12), (15) doubt that

vicarious removal of nitrogenous products takes place through the skin when kidney function is impaired. The finding of a high concentration of nitrogen in nephritic sweat points to the possibility, however, that sweat may serve as a valuable vehicle for excretion of nitrogenous substances in this condition. Further work will be necessary before a final explanation of all the benefits that accrue from sweating is forthcoming.

In a somewhat parallel connection it is of interest to ascertain whether in cases of nephritis accompanied by acidosis, the acidosis expresses itself in terms of an acid sweat. It is accepted that acidosis constitutes a part of the pathological picture in some cases of nephritis. Observations were therefore carried out on one case of nephritis which was definitely acidotic and, in addition, on three cases with edema and on four others with nitrogen retention. The range of pH was found to be about the same as that encountered in normal sweat and there

TABLE VI  
Sweat in Nephritis

No	Fore-head sweat pH	Bag sweat pH	Total N mgs per 100 cc	BUN mgs per 100 cc	No	Fore-head sweat pH	Bag sweat pH	Total N mgs per 100 cc	BUN mgs per 100 cc
3*	4.8	4.8	—	—	8	7.8	—	256	55
4*	4.8	4.8	—	—	1**	8.0	—	517	—
5	5.0	4.8	288	—	9***	8.0	7.4	—	—
10	6.2	6.0	84	22	7	—	6.6	482	90
2*	7.4	6.6	262	117	11	—	7.0	108	—
6	7.6	5.0	—	45					

\*Edema

\*\*Hemorrhagic nephritis

\*\*\*Edema, Plasma pH 7.21

was, therefore, no suggestion that nephritic acidosis induces an acid sweat. The bag sweat of case No 9 (blood plasma pH 7.21) had a pH of 7.4 and the forehead sweat had a pH of 8.0.

#### SWEAT IN SCLERODERMA AND PSORIASIS

The observations in Tables VII and VIII are on the sweat collected from cases of two skin diseases that seem to have something in common, pathologically, with arthritis.

The number of cases studied does not justify much emphasis but in the few observations that have been made there is no indication of deviation from normal in the reaction of sweat in either scleroderma or psoriasis, though in subject "T" (scleroderma) the initial forehead sweat, collected at the beginning of sweating, was distinctly acid, pH 4.8 and pH 5.3. In psoriasis it was quite noticeable that no sweating occurred on the site of the active skin lesion, irrespective of the presence or absence of scales. This was ob-

TABLE VII  
Sweat in Scleroderma

Subject	Date	Forehead	Sweat	Bag Sweat pH	Total N mgs per 100 cc	
		Initial pH	Final pH			
T	2/9	4.8	6.8	5.6	295	improved
T	2/12	5.2	6.0	5.6	292	
T	2/15	5.3	6.4	6.0	178	
T	2/27	4.8	5.8	5.0	224	
T	3/22	4.8	7.0	5.4	143	
B		8.0	8.4	6.7	140	
M		7.8	7.8	7.0	133	
K				6.4	101	

TABLE VIII  
Sweat in Psoriasis

No	Site	Unaffected healthy areas pH	Partly healed areas pH	Total N mgs per 100 cc
1	forehead	6.8	6.8	50
2	forehead	7.3	5.8	82
3	forehead	7.5	7.0	66
4	forehead	7.0	6.4	
5	forehead	7.4	7.6	
6	abdomen	7.6	6.8	

served repeatedly on every case examined. Psoriatic patches that were partly healed showed less active sweat secretion than did clear skin areas. In several cases the sweat collected from partly healed areas was more acid than sweat from uninvolved neighboring areas. Barney (16) found the concentration of the non-protein nitrogen and the sodium chloride in the sweat of psoriatics to be the same as in the sweat of normal persons. In one case of scleroderma observed by us over a period of several months, the sweat nitrogen, high at first, progressively decreased coincident with clinical improvement. In three other cases of scleroderma the content of nitrogen in sweat was not found to be conspicuously high.

#### SUMMARY

The total carbon dioxide content of sweat has been determined and the effect of its removal by aeration and boiling on the reaction of sweat has been studied.

Acid sweats were found to contain only very small amounts of  $\text{CO}_2$  and their reaction was usually not affected by boiling or aerating the sweat. Such sweats appear to be acid because of some component other than  $\text{CO}_2$ . Alkaline sweats contain more  $\text{CO}_2$ . Endeavors to relate the reaction of sweat to its content of fatty acids or

phosphoric acid were not successful. The cause of the acidity of sweat remains to be determined. The change in reaction of sweat during long continued sweating, as during therapeutic body bakes, etc., seems to be the result of actual excretion of alkaline substances.

The nitrogen and chloride content of arthritic sweat was not found to be different from the data available in these respects for normal sweat.

The sweat from a few cases of nephritis was examined. In the majority of these an abnormally high nitrogen was encountered. In spite of the doubt of some workers that vicarious elimination of nitrogenous substances takes place through the skin, these figures suggest the possibility that in nephritis the skin may serve as a valuable path for the excretion of nitrogenous substances. The reaction was similar to that found in other persons.

In psoriasis, no sweating appeared over the involved areas and the amount on partly healed areas was less than that on nearby clear skin areas. The reaction and nitrogen content of psoriatic sweat showed no abnormalities. It was observed that the sweat from partly healed areas frequently was more acid than sweat from areas unaffected with psoriasis.

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# Sclerosis of the Coronary Arteries of the Heart

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INASMUCH as arteriosclerosis itself forms one of the important problems for investigation for both the clinician and pathologist it would seem that any further investigations made with the object of observing in more detail all changes found in the vessel walls would always be opportune. For the present study our observations have been directed toward the coronary arteries of the heart. Our object was to determine how many different types of sclerosis occur in the coronary system, the nature and distribution of these types of sclerosis, and the effect of certain diseases upon the frequency of occurrence of coronary sclerosis.

The material used consisted of a series of unselected hearts from individuals of all ages who came to necropsy in the Toronto General Hospital during the term 1925 to 1926. Ninety-five hearts were thus collected and studied. Gross descriptions were made of the condition of the coronaries and their branches. Sections for microscopic study were then made from the main stems of both coronaries, from the distal portions of both circumflex branches, and from the terminal portions of the anterior descending branches of both circumflex arteries. The muscular branches were

studied in sections of the anterior papillary muscle of the left ventricle, and from portions of heart attached to the sections of the descending branches. In certain cases other portions of the coronary system were carefully sectioned as well, particularly where, either from the clinical history or gross findings changes were suspected in certain other areas. The blocks were fixed in 10 percent formalin and embedded in paraffin before cutting with the microtome. Staining was done as a routine by two methods: (a) Haematoxylin and Eosin, and (b) Weigert's Haematoxylin for the elastic tissue. In certain cases Zenker-fixed material was used and sections cut from these were stained by Mallory's phosphotungstic acid haematoxylin or Van Gieson's stains. In selected cases some sections were cut with the freezing microtome and stained with sudan III and haematoxylin to demonstrate fatty changes. This study was correlated further by keeping an accurate record of the arteriosclerotic changes found elsewhere in the body. Records were kept of the clinical signs and symptoms leading to a diagnosis in each case, together with the age, sex, habits, past illnesses, and the blood pressure findings. It was only in this way we could gauge the



true importance of any pathological findings observed

The term "arteriosclerosis" as Klotz has often pointed out should include any hardening or thickening of the vessel wall. This has the advantage of allowing the clinician to use the same term rather widely for a variety of conditions which frequently the pathologist alone is able to analyze accurately. Under such a term, then, one may include proliferative as well as degenerative conditions, and often the two are combined.

The anatomy and histology of the coronary arteries has recently received considerable attention from investigators in different countries. The consensus of opinion seems to be that the two coronaries communicate freely through their smaller branches, forming a wide meshwork of arterioles and capillaries. The coronary arteries belong to the muscular type of artery with three coats, the intima, the media, and the adventitia. Before Edholm in 1912 reported his studies little or nothing was written as to the normal histology of the coronary vessels. Faber in the same year published a monograph supplementing Edholm's work, little more appeared until Wolkoff in 1923 published his study of nine hearts of different ages. Our work supported the following views. (a) the small muscular arteries of the myocardium and the small epicardial arteries have a similar histological character in normal healthy individuals, i.e. an intima bounded internally by a single layer of endothelial cells and externally by a wavy internal elastic lamina, between which there is only a small amount of fine

fibrous tissue. In the intima of the smallest arteries there is no fibrous tissue. The internal elastic lamina as McMeans has pointed out, consists of an acellular band of homogeneous material which under certain conditions will split and disclose its inner composition. This seems to be a laminated structure of fine fibrillar material. McMeans has shown that any inflammatory or toxic substance acting in sufficient concentration results in a dissolution or alteration in the sheath of this elastic lamina and gives the appearance of splitting. Any splitting or alteration of this sort, once induced is permanent, and may be increased by further injury. In these smaller arteries, as a rule, the internal elastic lamina is unbroken and appears as a faintly eosin-staining wavy band encircling the intima either in longitudinal or cross section.

The media, made up of involuntary smooth muscle fibres, varies in its thickness with the diameter of the lumen. Between the muscle fibres which run in a circular direction is a small amount of fine fibrous tissue with few collagen fibres but often showing a small number of fine elastic fibrils. The external coat or adventitia consists of loose connective tissue bundles made up of collagen fibres intermixed with a considerable number of elastic fibrils and some muscle cells. As a rule this coat in the smaller arteries is two or three times the thickness of the media. The elastic tissue rarely forms a true external elastic lamina. In the medium-sized arteries (a group usually constituted by the descending and circumflex branches of the coronaries which run in the epi-

cardial fat), the intima presents a few longitudinal muscle fibres lying internal to the internal elastic lamina

The main coronary arteries, right and left, constitute the group of larger arteries. Their coats follow roughly the same proportionate sizes to one another as those in the medium-sized group. Small nutrient vessels and sympathetic nerve fibres are nearly always found throughout the adventitia of these main stems. It has not been possible to determine definitely how far inwards these nutrient vessels pass in a normal coronary, but in many cases showing sclerosis these have grown through the wall into the intima. Wolkoff's work gives very good descriptions of the vessels studied, but in the main they showed arteriosclerotic changes. He considered a splitting of the internal elastic lamina, at least in the larger arteries, as a normal condition for a mature artery and went so far as to say that a completely developed intima probably has three layers of elastic and connective tissue in it. We would, on the other hand, insist on the intact internal elastic lamina and the above described characteristic coats as those belonging to a normal artery. Inasmuch as in certain cases also, we have been able to demonstrate arteries from elderly individuals which do not show this complicated type of intima while in others where disease has been or is still acting we have seen it appear at a very early age we do not feel justified in considering all such changes as the normal consequence of age. Jores called a splitting of the elastic lamina and any hypertrophy of the internal longitudinal muscle layer, arteriosclerosis

We, however, would call any thickening of any one of the three coats a type of arteriosclerosis

*Types of Sclerosis Occurring in the Coronary Vessels* In our series a great preponderance was found in the frequency of intimal changes, as compared to the sclerosis of the other coats. This held true in all the coronary vessels except the small muscular or finest subepicardial twigs, in which a thickening of the adventitia formed the commoner type of lesion. Chronic nodular or diffuse endarteritis is by far the most common type of sclerosis in the coronaries of the heart. The early changes observed in this lesion seem to consist of one of two things (a) a deposition, layer upon layer, of the endothelial lining, and (b) an increase in the delicate sub-endothelial connective tissue stroma. The latter may be small at first, and may be accompanied by a mild infiltration from the lumen of large mononuclear cells and lymphocytes. At times this connective tissue increase is definitely made up of collagen fibres, while at other times there seems to be a clear, homogeneous material with relatively few fibroblastic cells. This would lead one to suspect that the endothelial cells have laid down some type of matrix. These fibres may show further changes, often becoming swollen, and pale staining, and at other times appearing hyaline. Frequently these areas seem to undergo a bland necrosis, losing their staining ability and appearing as a fine reticulated debris as though all the original substance were gone and only the skeleton of the fibres remained. These areas show practical-

ly no accompanying cellular infiltration. Other areas of the artery, however, show that the cellular infiltration has progressed through the entire depth of the intima. If the individual has suffered a severe purulent infection, it is commonly manifested by increased numbers of polymorphonuclears and other inflammatory cells in the intima itself. Not uncommonly one can make out the signs of an acute endarteritis superimposed upon a chronic endarteritis. In our study of the coronaries we found the presence of vasa vasora in the intima in the more marked cases of nodular endarteritis, and not necessarily related to a syphilitic process. Other changes may and usually do occur as time goes on in the nodular thickening of the intima. One of the first of these is the fatty change so commonly seen. When an undue amount of fat is present within a cell or its fibrillar processes one may speak of it as "fatty degeneration" (Klotz). This often occurs in the collagen fibres of the much thickened intima. When the fat in these cells and in the stroma is freed by destructive processes one is confronted by a different condition. Such a state is spoken of as "atheroma" and is recognized both macroscopically and microscopically as a gruelly mass of fat, protoplasmic detritus and cholesterol crystals. From our study it is probable that every type of cell in the intima may undergo fatty degeneration at one time and another and such an accumulation of fat can be disposed of only by chemical combinations with the tissue fluids. The process of calcification has been investigated by Klotz who states that while soluble

compounds of the fatty acids and cholesterol esters may be formed, the insoluble calcium and magnesium soaps occur just as frequently. Calcification then is a stage in the degenerative process. The calcium deposits occurred nearly always in association with atheromatous changes. Associated with these processes fine calcium granules may appear in the hyaline areas of the connective tissue in the intima.

Chronic nodular endarteritis as stated above forms the largest group of sclerotic changes found in the coronaries. In the gross these arteries vary from the barely palpable thickenings, to the group of very tortuous nodularly thickened vessels, almost pipestem in hardness. These may be irregularly hardened, some areas being entirely encircled by a calcareous ring, whilst other areas are not. The case may be conveniently subdivided into (a) chronic nodular or diffuse endarteritis (1) simple, (2) with early fatty degeneration, (3) with hyaline degeneration, (4) with atheroma, (5) with calcification. There of course may be any combination of these present. A discussion of the incidence of these will appear later. In certain cases notably those in which the individual has suffered some acute infection one finds in the gross some delicate yellow streakings in the intima. These may run lengthwise or appear as oval areas. They are seldom palpable. These, if sectioned, preferably with the freezing microtome, show the presence of large, pale, oval or round cells with a foamy vacuolated cytoplasm in the centre of which is a small round nucleus. These cells have been called foam cells and while filled with large

amounts of lipoids and cholesterol esters, still are to be differentiated from atheroma. Large numbers of these cells recupurate and the fatty streaks in the gross tend to disappear. Such fatty change in the coronaries, occurs mainly in the intimal tissues although a few have been observed in the media. Only rarely were these observed in the coronaries apart from a similar condition in the aorta.

*Changes in the Musculo-Elastic Layer* As mentioned above we do not agree with Wolkoff that a marked change in the musculo-elastic layer is to be considered as a simple age phenomenon. We would draw attention to the fact that the cases described by him were those of septicaemia, scarlet fever, pneumonia, uterine rupture, and fibrino-purulent peritonitis etc. We would expect such cases to show inflammatory changes in the intima or media, and in view of McMean's work, the internal elastic lamina would also probably show longitudinal splitting. We have observed cases of aged individuals whose arteries did not show these changes, and on the other hand, arteries from a fourteen year old child which did show them to a marked degree. The process underlying a hypertrophy of the internal longitudinal muscle layer of the intima is not as yet fully understood. We have observed a marked hypertrophy of this layer at the early age of five days, and at succeeding ages upwards. One notable case seeming to support Jores' theory that hypertension results in a hypertrophy of this layer, was found in an individual of twenty one years (A-184-25) who suffered a condition of congenital absence of the main pul-

monary artery. Both ventricles opened into a common aorta, and a pressure of 250 mm Hg was found clinically in the right brachial artery. At autopsy the arteries stood out as tortuous and tremendously thickened vessels. On examination we were surprised to find that the thickening was mainly due to a marked hypertrophy of the musculo-elastic layer. Numerous other cases of hypertension were examined in which one was unable to demonstrate a similar change.

As a rule, the changes in the musculo-elastic layer are as follows: the internal elastic lamina splits into two layers which become separated by a few longitudinally running muscle fibres, a small amount of connective tissue and occasionally some foam cells. The inner of these two layers, which is called "the grenzelamella" (Jores, Torhorst, Wolkoff), then undergoes further splitting. This results in a layer of irregular circularly disposed strands of elastic tissue. The whole mass lying between the split elastic fibres constitutes the hyperplastic layer of Jores. As the individual advances in years, certain changes seem to occur whereby this hyperplastic layer becomes altered and more difficult to stain until finally very little elastic tissue can be demonstrated in the senile artery. Early changes in the internal elastic lamina may be hard to recognize. As McMeans has pointed out for other arteries, the changes consist of a granular appearance, some swelling, or slight variation in staining qualities. Other changes are easily seen, such as a clumping of the elastin in a granular manner, and a little later calcification of this structure frequent-

ly occurs. It is possible that certain fatty changes may precede this calcification of the lamina. One of our cases aged twenty three years showed this calcification of the internal elastic lamina to a marked degree. This was one of the youngest cases showing calcium deposits in the coronaries and was present in the internal elastic lamina, but not elsewhere in the artery.

*Changes in the Media* A mesarteritis of the coronary does not occur nearly as frequently as an endarteritis. It may consist simply of an inflammatory reaction so frequently seen accompanying acute systemic infections. In such cases, small aggregations of inflammatory cells, lymphocytes, endothelials, plasma cells, and occasionally some polymorphonuclears are found. These are usually in association with the vasa vasora. Syphilitic or rheumatic mesarteritis as described in the aorta by Klotz, Pappenheimer and Von Glahn are not nearly as easily recognized in the coronaries as in the aorta. Healing of such cases of mesarteritis as does occur is by fibrosis. It is probable that certain cases of severe intoxication result in cloudy swelling and degeneration of the muscle fibres in the media. These too may be replaced by fibrosis. Feytre in 1925 reported a case of myomalacia cordis in which this fibrosis of the media was a marked condition. Schmiedl described a similar condition in the superior mesenteric artery. Usually the fibrosis is more marked on the outer side of the media, as though it were derived from the adventitia. At other times nearly the whole thickness of the media is af-

ected. This type of lesion progresses further along the coronaries, towards the finer ramifications than any other type. Usually there is some slight increase in the elastic fibres too.

Besides this fibrosis one frequently notes a great thinning and atrophy of the media beneath the area of nodular endarteritis. MacCordick studying the radial artery, found medial atrophy in cases of pernicious anemia, and other wasting diseases. In some cases he found hypertrophy and hyperplasia with chronic nephritis and hypertension. Moreover he noted such medial changes without accompanying changes necessarily being present in the intima. Although exact measurements as done by him were beyond the scope of this work, yet some attention was paid to this, with the result that no thinning or atrophy was found apart from the nodular intimal thickening. No localized hypertrophy of the media was found. Thinning of the media may be explained by the fact that an increase in the thickness of the intima reduces the nutrition to the inner part of the media, which derives its supply mainly through diffusion from the lumen. Then the pressure, whether normal or increased, acting on the weakened wall may result in a stretching and gradual thinning as is so frequently noted behind the nodular thickening. No area of calcification or atheroma was observed in the media. No case of medial calcification of the coronaries of the heart was found in the literature, and from our own experience we are safe in concluding that "Moenckeberg's sclerosis," the type so frequently found clinically in the

peripheral vessels, rarely if ever occurs in the arteries of the heart

*Adventitial Changes* Adventitial changes in the coronaries, either in the large or small branches are usually inflammatory in nature, and are accompanied by the various inflammatory cells depending on the type and severity of the reaction. In the finest twigs running in the epicardial fat or in the muscular branches, particularly those in the papillary muscles, one may find a marked fibrosis. This may be either the healing or healed stage of a previous inflammatory condition in the adventitia, a type common to the finest branches. This fibrosis of the adventitia invades the media and in this minute type of artery the media may be almost completely replaced by fibrous tissue. As this fibrosis contracts, it tends to narrow the lumen of the arteries and results in nutritional disturbances in the surrounding heart muscle. As the muscle fibres are injured by such vascular changes, they are replaced by new fibrous tissue, the result of which is an increase of the areas of fibrosis in the myocardium. It is probable that the majority of the cases of this type of sclerosis are related to rheumatic fever and syphilis. Thalheimer and Rothschild believe that many of these small fibroses represent healed Aschoff bodies. Nutritional disturbances to the heart muscle likewise may result from arterial changes (nodular endarteritis) in the proximal portion of the left coronary and its anterior descending branch, which are the commonest sites for such a lesion and may account for the greater preponderance of myocardial fibrosis seen in the septum.

*Age Appearance of Sclerosis* Accepting the definition of arteriosclerosis as laid down in the beginning of this paper, we found sclerosis present at the early age of five days. This case (A-42-26) was that of an infant of normal birth who vomited for five days and died. At autopsy an anomaly of the duodenum was found wherein no connection between it and the jejunum was present. Both the right and left coronary arteries in this case showed a nodular thickening of the intima which proved to be an hypertrophy of the musculo-elastic layer of the intima. This hypertrophy was more marked in the left coronary where the internal elastic lamina was also split. Cases of marked sclerosis were also found at the ages of 14, 16, and 20 years respectively. From then on sclerosis in one or more form to a varying degree was found in nearly every case. The earliest occurrence of calcium deposit was in the internal elastic lamina of the coronary artery, at the age of 23 years. The earliest case of atheroma was aged 23 years. Calcification of the intima did not commonly occur before 50 years. The youngest case in which a definite adventitial fibrosis of the muscular arteries was present was 16 years of age. Cases of arteriosclerosis occurring in early life are not unique (Freemont and Smith, Durant, Meigs, Hodgson, Adler and Wiesner, Bryant and White).

Analysis of Table I shows that the frequency of arterial changes in the coronaries of the heart increases with age up to 50 years after which practically every one shows some sclerosis of the coronary arteries. Moreover

TABLE I

Age periods of cases studied	Years 1-20	21-30	31-40	41-50	51-60	61-70	over 71
Number of cases studied	14	6	15	16	18	17	9
Coronary sclerosis (all grades)	4	3	10	12	17	17	9
Fibrosis of adventitia	3	2	8	5	10	8	6
Atheroma	0	1	4	6	11	13	6
Calcification	0	1	1	3	10	10	5
Sudden death	0	0	1	1	4	3	3
High Blood pressure	0	1	1	3	4	5	3
Hypertrophy of the musculo-elastic layer	2	2	0	1	3	2	0
Medial fibrosis	1	1	3	3	4	5	4
Percentage of examined cases showing cerebral sclerosis	0	0	16	50	57	100	100

chronic nodular endarteritis is by far the most common lesion observed. Calcification and atheroma appear as the late degenerative changes and are seldom seen under 30 years. Neither of these occurred apart from chronic nodular endarteritis, and atheroma itself occurs slightly more frequently than calcification. Fibrosis of the adventitia in the small arterioles and muscular branches is seen either with or without gross fibrosis in the myocardium. Such a type of lesion rarely is seen under 30 years and progressively increases with age. It is usually associated with endarterial changes in the larger trunks of the coronaries but not necessarily so (Anitschkow, Fischer, Martinotti, Mircoli and Bonome). Inflammatory changes appear to be distributed more or less uniformly along the course of the coronaries and may occur at any age. Seventeen

cases with a systolic blood pressure of 150 mm Hg or over were studied but no arterial changes characteristic of increased blood pressure were found. Thirty cases died of some acute illness. These showed recent inflammatory changes in the various coats. It is likely that acute infections as well as rheumatic fever give rise to an increased number of arteriosclerotic cases (Klotz, Thayer and Brush).

*Relation of Sclerosis of the Coronary Arteries to Sclerosis Elsewhere*  
Another interesting point is observed in the comparison of the prevalence of coronary sclerosis with the incidence of sclerosis elsewhere. Willius and Brown have given us a series of figures which are compared with our own in Table II.

The data obtained by Willius and Brown in the study of coronary sclerosis was analysed from quite a

TABLE II

	Our series of 95 cases	Willius and Brown's series of 86 cases
Coronary sclerosis occurred in	76%	100%
Cerebral sclerosis occurred in	52%	86%
Aortic sclerosis occurred in	92%	99%
Valvular changes occurred in	67%	51%
Lesions of myocardium occurred in	43%	100%*
Renal sclerosis occurred in	25%	37%
Peripheral sclerosis occurred in	22%	70%
Infarcts myocardium occurred in	2%	8%
Accessory coronary arteries occurred in	13%	
Sudden death due to cardio-vascular causes occurred in	13%	37%

\*Willius and Brown include cloudy swelling segmentation, fragmentation, fatty degenerations, etc, hence their figures are scarcely comparable with ours

different angle than those of our own. Their series of eighty-six cases were chosen for the study of an obvious coronary sclerosis to obtain the relationship between this lesion and the clinical manifestations in the patient. We, on the other hand, were desirous of determining the manner of development of coronary sclerosis of all cases. Hence, apparent discrepancies appear in the comparison of our figures, for as they state in their article, the average age of the patient in their series was sixty years, while ours was in the forties. The increasing incidence of all forms of sclerosis in the ascending decades of life is well illustrated in the comparison of the two series of cases.

#### SUMMARY

(1) Coronary sclerosis is the second commonest type of arteriosclerosis which we have encountered. It cannot be gauged by examination of the peripheral arteries alone.

(2) The distribution of sclerotic changes in the coronaries of the heart

varies widely according to the portion of this arterial system examined. Intimal changes occur most frequently in the main coronaries, less frequently in the larger branches, and are seldom seen in the fine muscular twigs. Adventitial changes on the other hand are more common in the finer muscular branches.

(3) Coronary sclerosis is usually present in both coronaries. It is more marked however, in the left coronary than the right.

(4) Nodular endarteritis is the most common lesion affecting the coronary arteries of the heart, and it often produces marked obstruction to the lumen. It rarely occurs apart from an aortic sclerosis.

(5) Atheroma and calcification of the intima of the coronaries rarely occur in the smaller branches. This lesion increases in frequency with age and is nearly always secondary to a chronic nodular endarteritis.

(6) Fatty degenerations may occur in any portion of the intima or media



Fatty streaks in the intima are usually found associated with intoxications, acute infectious diseases and metabolic disturbances

(7) Calcification of the internal elastic lamina when it occurs, may be the only calcified area in the artery

(8) Acute systemic infections are evidenced in the coronaries of the heart by cellular reactions in the various coats. As a rule these are more marked in the adventitia and intima than in the media

(9) The most common lesion in the finer muscular branches and epicardial twigs is an increase in the connective tissue about the adventitia

(10) Fibrosis of the myocardium is probably largely an end result of coronary disease, especially the fibrosis occurring around the finest vessels which

is related to an adventitial type of sclerosis

(11) The most common site for coronary occlusion is at the commencement of the anterior descending branch of the left coronary. The occlusion is nearly always the result of a process of thrombosis. Nodular endarteritis or atheromatous changes alone rarely, if ever, produce occlusion

(12) Occlusion of one coronary, if not too suddenly produced, results in so-called "anemic infarcts," which may heal by fibrosis

(13) The symptom-complex, angina pectoris, is commonly related to coronary sclerosis

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# Gastric Tuberculosis With Report of Two Cases\*

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**T**UBERCULOSIS of the stomach is seldom encountered and practically never diagnosed clinically. Two instances of it are on record at the University of Michigan Hospital. In a series of 2900 consecutive autopsies, one case was encountered. In the routine pathological examination of surgical specimens, another case has recently been found.

Broders of the Mayo Clinic made an exhaustive review and analysis of the literature on the subject in 1917. He reported the single case occurring in their series of 2501 gastric operations. His analysis included 305 published cases, in addition to his own. He divided the cases into four groups, as follows:

1 Positive cases. Those which present an histologic picture of tuberculosis plus the presence of the tubercle bacillus in the depths of the lesion, or the presence of the specific bacillus in the depths of an indefinite histologic lesion.

2 Probable cases. All cases that possess an histologic picture of tuberculosis.

3 Doubtful cases. All those with a

good gross description of tuberculosis or a good gross description plus a poor histologic description.

4 Rejected cases. Those that cannot meet the qualifications of the three preceding classes.

It is interesting to note that in only 49, or 16 per cent of the cases analyzed by Broders, were tubercle bacilli demonstrated, establishing what he would call a positive diagnosis. In 118 more cases, or 38.8 per cent of those reviewed, the histologic picture was that of tuberculosis. It thus becomes apparent that nearly half the cases reported were to be classified as doubtful or rejected. It was further shown in this analysis that adults were affected more often than children, the ratio being about 3 to 1. Males were affected more often than females, the ratio being 2 to 1. Ulcer was the predominating lesion in the positive and probable cases, constituting 81.6 per cent of the former and 80.5 per cent of the latter. In the positive cases the lesser curvature was the most frequent site of the ulcer or ulcers, and the pylorus the most common site in the probable cases and in a combination of the positive and probable cases. In tuberculosis or other organs associated with gastric tuberculosis, the lungs were most commonly affect-

\*From the Department of Pathology, University of Michigan. Service of Dr Warthin.

ed (69 per cent of positive and 86 per cent of probable cases), closely followed by the intestines (59 per cent of positive and 69 per cent of probable cases) Broders further pointed out that no case of tuberculosis of the stomach had been absolutely proved to be primary in the stomach

Razzaboni in 1919 reported a case in which subtotal gastrectomy was done on a woman 60 years old, with a typical clinical picture of gastric carcinoma The greater part of the tumor was on the lesser curvature, but it infiltrated most of the stomach On the inside of the stomach there was an ulcer crater larger than a dollar, with margins deep, hard and distinct Microscopical sections showed the typical histologic picture of tuberculosis in the base of the ulcer, some distance from the ulcer and in omental lymph nodes Tubercle bacilli could not be stained, but fortunately the material was handled in such a manner that it was possible to use some of it for animal inoculation This showed the lesion to be definitely tuberculous Razzaboni's patient was apparently in good health three and one half years after operation

Geuken in 1920 published an account of a patient 35 years old who had had pleurisy two years before the onset of gastric complaints At operation "a hard string of tuberculous tissue was compressing the stomach in several places, whilst in the forewall of the stomach were to be found tuberculous foci Four years afterward the patient died of general tuberculosis" The author did not record the histologic examination

Suemondt in 1925 found after resection of a gastric ulcer that it was an exclusively tuberculous process, with connected cheesy glands No other manifestations of tuberculosis were discovered elsewhere but roentgenoscopy revealed traces of an apparently healed small tuberculous focus in the right lung

In 1925 Hurst reported with some detail the case of a man 46 years old with a history of ten years of epigastric pain There was nearly complete achlorhydria and always occult blood in the stools X-rays of the chest were suggestive of chronic tuberculous disease. There was no pyrexia and the Wassermann test was negative X-rays of the stomach showed an irregular ulcer crater suggestive of malignant degeneration Examination of the lesion after partial gastrectomy revealed what appeared to be a simple ulcer three-fourths of an inch in diameter, a little below the middle of the lesser curvature. Sections showed a tuberculous process occupying the thickened margins of the ulcer and infiltrating the surrounding regions The tubercles were typical and occurred freely in the mucosa and submucosa, the wall beneath being thickened by fibrous tissue. Hurst concluded that the condition was caused by secondary infection of a chronic gastric ulcer with tubercle bacilli from swallowed sputum He did not state the results of any search for tubercle bacilli in the lesion

In 1925 Lundgren showed at autopsy that a dilatation of the esophagus in a man 55 years old, which had been thought to be due to cardiospasm, was the result of a nodular tuberculous

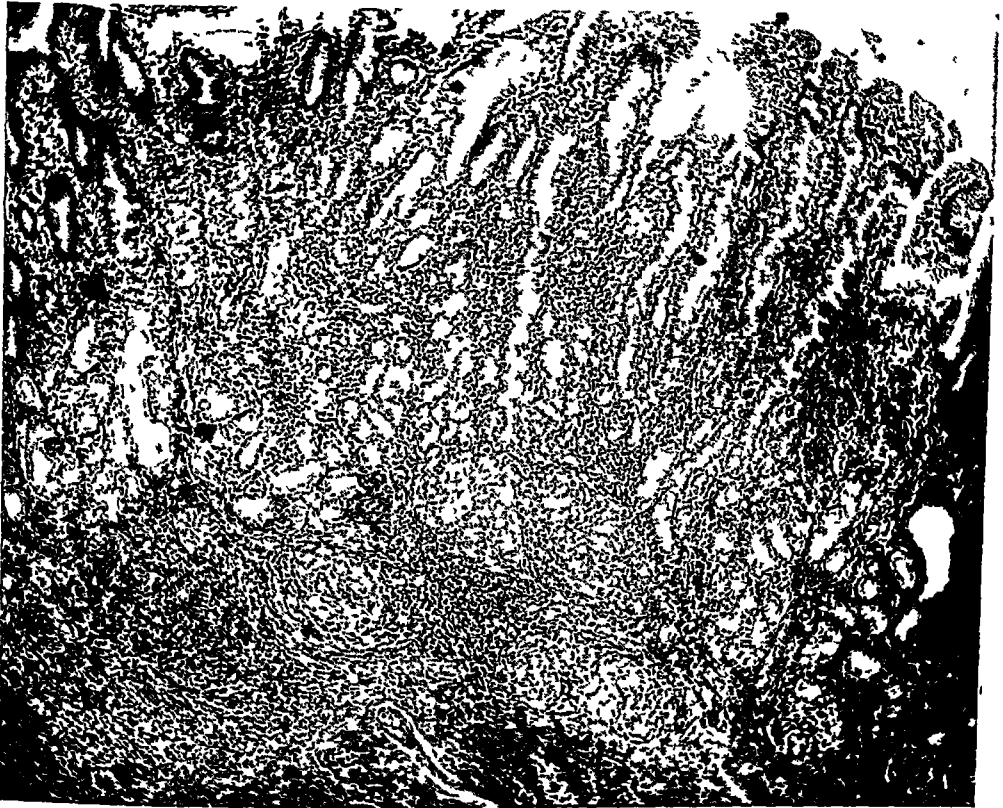


FIG 1 Low power view of stomach mucosa at border of ulcer, showing a group of miliary tubercles in submucosa, and small one in mucosa

process of the cardia of the stomach. A good histologic description was presented, but apparently tubercle bacilli were not demonstrated.

Faltin in 1927 demonstrated an adenocarcinoma developing at the border of a large tuberculous ulcer in the stomach of a man 62 years old. The patient had had pulmonary trouble for years, but tubercle bacilli never could be found in the sputum. The lymph glands along the lesser curvature were also tuberculous. Prior to operation marked hyperacidity and disturbed motility of the stomach were demonstrated. The author believed the adenocarcinoma was secondary to the tuberculous ulceration.

Collinson and Stewart in 1928 found tuberculous ulceration of the stomach in only three cases out of a series of 10,000 autopsies at the Leeds Infirmary, and "in two of these it was due to involvement from without by adjacent tuberculous lymph glands. In a series of 320 partial gastrectomies in which the specimens were examined microscopically, none were the seat of tuberculous ulceration, but in two cases a simple chronic ulcer was associated with scattered miliary tubercles throughout the mucosa, while in a third, typical 'carcinoma ex ulcere' co-existed with a lesion at least strongly suggestive of tubercle." The latter case occurred in a man 31 years old. The



FIG 2 Higher power view of preceding, showing group of miliary tubercles in mucosa and submucosa

other two surgical cases were in women aged 57 and 45 years. Excellent histologic evidence was shown of tuberculosis. Prolonged search for tubercle bacilli, however, was futile. The authors showed by their statistics that the type of person who develops a gastric or duodenal ulcer is less commonly the subject of tuberculous infection than the general population.

#### ROUTES OF INFECTION AND RELATIVE IMMUNITY

Willerding has summed up the possibilities by which the stomach may become infected with tuberculosis, as follows: (1) hematogenous, (2) lymphogenous, (3) transserosa, (4) from

swallowed sputum in pulmonary tuberculosis, (5) by antiperistalsis from tuberculous enteritis.

It has been stated that in order to infect the mucosa a break in the continuity of the mucosa and a decrease in the acidity of the gastric contents are necessary (Duerck). We are fairly willing to grant that the first, that is, a break in the continuity of the mucosa, is necessary. However, the work of Zagari, Strauss and Wuertz, Carrière, and others has shown definitely that the virulence of tubercle bacilli is scarcely affected unless they are in contact with gastric juice for at least twelve hours.

Arloing was unable to produce tuberculous gastric ulcers in animals

when, after introducing human tubercle bacilli into their stomachs through fistulae or mucosal inoculations, he changed the acidity to strongly acid and strongly alkaline, ligated arteries along the greater curvature, and produced ulcerations of the mucosa by the electric needle and mucosal injections of an emetic. In another series he injected tubercle bacilli intravascularly and produced gastric ulcers, which however, were not definitely tuberculous. He did produce two tuberculous duodenal ulcers in dogs by this method, and all of his animals showed polyvisceral miliary lesions. In still another series, by means of interstitial inoculation of the gastric wall, he was occasionally able to produce tuberculous ulceration.

It is interesting to note that in a case reported by Hoppell and Blumer, the patient had advanced pulmonary tuberculosis, chronic gastric ulcers, and an absence of free hydrochloric acid in the gastric contents. Microscopic examination of the ulcers showed tubercle bacilli over the surface, but in the depths of the ulcers there were neither tubercle bacilli nor tubercles.

There has been considerable difficulty in deciding in some cases whether a tuberculous ulceration had been set up opposite adherent tuberculous glands, or whether the adherent glands were infected through the lymphatics from the region of the primary infected ulcer. It seems possible that either of these might occur.

There are several cases on record in which there is little doubt that the gastric wall has been involved through continuity and contiguity of structure.

It is not uncommon, at autopsy, in cases of advanced peritoneal tuberculosis, to see the stomach cemented to the liver, spleen, diaphragm, pancreas and intestines by solid caseous material, yet the rarity with which the gastric wall itself is really involved in these cases is remarkable. It is a commonly accepted fact that the two tissues most rarely infected with tuberculosis are muscle and fat. In these cases of peritoneal tuberculosis, there is, of course, a tuberculous perigastritis. Between the serosa of the stomach and the musculature there are no lymph follicles, and it is doubtful whether there is any flow of lymph in the direction of serosa to mucosa. Assuming this to be true, the rarity of involvement of the gastric wall in cases of advanced peritoneal tuberculosis can be at least partially explained on the basis that there is an immune tissue, namely, muscle, between the infection and the site of election for the best growth of a tuberculous process,—the lymph follicles.

Hurst and others have concluded that the tuberculous involvement of the stomach in their cases was due to infection of chronic gastric ulcers by tubercle bacilli from swallowed sputum. Collinson and Stewart in 1928 presented the following statistics. In 1000 consecutive autopsies, 86 of the cadavers, or 8.6 per cent, were tuberculous. In autopsies on 151 cases of acute gastric and duodenal ulcer, 5 cadavers, or only 3.4 per cent, were found to have active tuberculosis. In autopsies on 282 cases of chronic ulcer or scarring of the stomach and duodenum, only 8 cases, or 2.8 per cent, had active tuberculosis. The conclu-





FIG 3 Miliary tubercles in submucosa near border of gastric ulcer

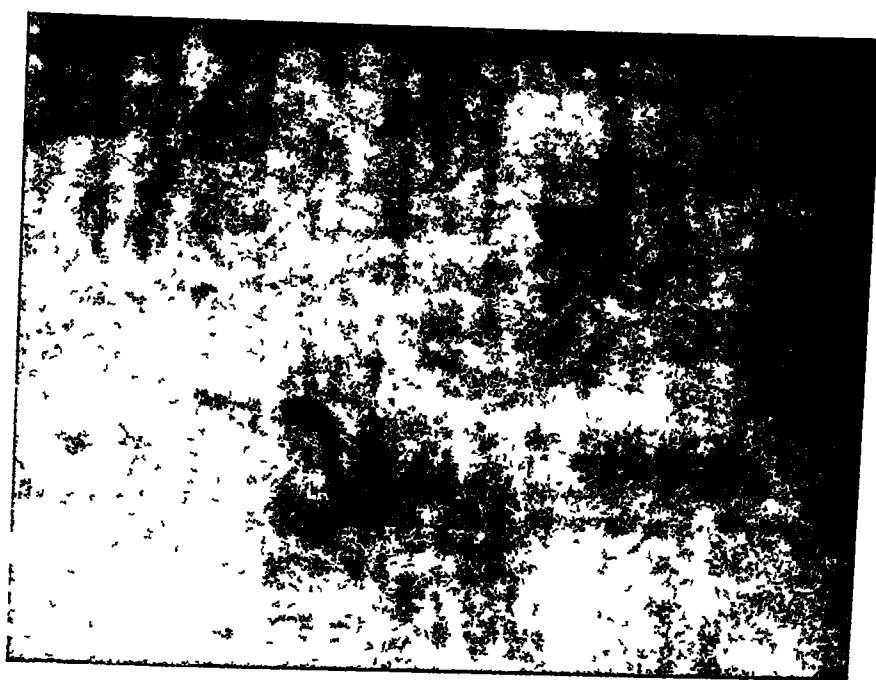


FIG 4 Oval acid-fast bodies in miliary tubercles of gastric mucosa Much's granules  
(?)  $\times 1500$

sion that one might draw from these figures and the addition of deductions such as Huist made relative to his case is that the rarity of gastric tuberculosis may be partially explained on the basis of constitutional peculiarities. The constitution which is likely to develop gastric ulcer is not the type that acquires tuberculosis readily.

It seems logical to us that the factor of speed of passage of infective material through the stomach is important in explaining the rarity of gastric tuberculosis. The view that tuberculous enteritis is usually the result of infection through the mucosa and Peyer's patches has perhaps the majority of those who have considered the question as its advocates. Yet it seems to be that the relative stasis,—the period of time during which a given bit of infective material may remain in contact with a given portion of mucosa, is an important factor. The slowness of passage of infective material plus the richness of the submucosa in lymph follicles, in explaining the frequency of tuberculous infection of the ileum, and us in concluding that the rarity of tuberculous infection of the stomach may be partly explained by the rapid emptying of its contents (by hyperperistalsis in some of the cases of ulcers of the lesser curvature when the patient is swallowing tuberculous sputum), and by the relative rarity of the lymph follicles of the stomach as compared to the rest of the intestinal tract.

#### CASE REPORT No. 1

E. S., case No. 199452, male, aged 55, a white American laborer was admitted to the Medical Service of the University of

Michigan Hospital August 2, 1928, complaining of cramps in the stomach.

*Present Illness* Following influenza in 1918, the patient began to have attacks of very severe pain in the pit of the stomach. The pains were sharp, radiated up under the sternum and were severe enough to double him up. They were not related to meals. They lasted five to fifteen minutes and were relieved by vomiting. The vomitus was sour, bitter and yellow. After the pain was gone the patient had a feeling of distension and soreness in the upper abdomen. The attacks of pain at first occurred only every two or three months, but increased in frequency so that recently they had occurred at least once a week and sometimes two or three times a day. The diffuse soreness and distress had been constant for the last few weeks. There was never any jaundice or clay colored stools. There was no history of contact with lead. Venereal disease was denied. The patient had never vomited blood or noted tarry stools. He had suffered a gradual loss of 20 pounds in weight during the past two years. His appetite had been poor for a year. He was not troubled by constipation, but had occasional slight attacks of diarrhoea.

*Past History* Whooping cough, chicken pox and diphtheria occurred during childhood. He had measles at the age of 20, typhoid at 39, and influenza at 45. There had never been any dyspnea, palpitation, pain in the chest, cough, hemoptysis or night-sweats. There never were any gastrointestinal symptoms aside from those in the present illness. There had been no genitourinary complaints, no disturbance of sleep or memory, no nervousness nor ataxia. The marital history was not remarkable. The only thing of note in the family history was that the patient's mother was thought to have died of tuberculosis at the age of 44.

*Physical Examination* The patient was a well developed, fairly well nourished male who appeared to be of his stated age, and intelligent. Pupillary reflexes were normal. Several teeth were missing and those present were carious with marked pyorrhea. There was no lead line. The tongue had a gray furred coat. The thorax was normal.

in size and shape. The rate, depth and character of respirations were normal. The heart was not enlarged, the beat was regular and of normal force. There was a loud blowing systolic murmur at the apex. There was no increase in width of retromammary dullness. The blood pressure was 148/90. The lungs showed no abnormality of tactile fremitus, resonance, voice or breath sounds. There was no tympany, dullness or flatness.

*Abdomen* There were no visible superficial veins. The level was slightly below that of the chest. The panniculus was thin. No patterns or peristaltic movements were noted. The abdomen was symmetrical. There were no pulsations, masses, spasm, herniae or fluid. Respiratory movements were normal. No viscera were palpable. There was tenderness in the epigastrium on deep pressure. There was no costovertebral angle tenderness. The *genitalia* showed no abnormalities. The *prostate* was apparently normal. The extremities were normal in every respect aside from a moderate arteriosclerosis. *Bones and joints* were apparently normal. There were no palpable lymph glands in the neck, axillae, groins or epitrochlear regions. There were no skin lesions.

*Neurologic Examination* was negative.

*Laboratory Findings* *Urine* Yellow in color, specific gravity varied from 1.013 to 1.024. There was never any albumin or sugar. Centrifuged sediment showed no red blood cells or casts. There were two or three white blood cells per high power field. *Stools* Medium brown, semi-formed. Benzidine and guaiac tests were repeatedly negative. No mucus, parasites or ova were found. *Blood* Hemoglobin, 104 per cent, leucocytes, 9,450 per cubic millimetre. The Kahn reaction was negative on the blood. *Gastric Analysis* The fasting specimen was greenish in color, contained no food, blood or mucus. Free acid was 25°, combined acid 11°, total acidity 36°. The specimen taken 45 minutes after the test meal showed some food, no blood or mucus. Free acid was 49°, combined 20°, total acidity 69°. The specimen 90 minutes after the test meal showed some food, no blood

or mucus, the free acid was 61°, combined 10°, total acidity 74°.

*X-Ray Findings upon Admission* *Lungs* There was an accentuation of the hilar shadows and bronchovascular markings. Numerous small calcified areas were seen in the outer margins of the hilar shadows. There was a small group of areas of increased density in the left apex. These findings were interpreted as indicative of an old pulmonary tuberculosis, activity to be determined through clinical examination. *Gastro-intestinal X-Rays* The gall bladder was well visualized. There was a constant defect in the lesser curvature, which had the appearance of an ulcer crater. The duodenal bulb appeared spastic and showed a persistent deformity due either to another ulcer or a reflex spasm from the gastric ulcer. There was 16 per cent retention at six hours. The caecum was movable and not tender. The appendix was visualized, fixed, segmented, and not tender.

*Course in Hospital* A diagnosis of chronic gastric ulcer was made. Surgical treatment was deemed advisable and on August 17, 1928, operation was performed under nitrous oxide anesthesia. Exploration revealed a moderate amount of perihepatitis. The gall bladder appeared normal and emptied easily. The spleen, large and small bowel were normal. The appendix was not felt. There was a scar on the anterior surface of the duodenum close to the pylorus characteristic of an old duodenal ulcer. On the lesser curvature of the stomach, 7 centimeters above the pylorus, was an ulcer with a crater 5 millimeters in diameter surrounded by 2 centimeters of induration. Partial gastrectomy was done, removing the lower third of the stomach. Closure was affected by the method of Polya, and the abdominal wall closed in layers.

The patient's convalescence was uneventful. He vomited twice on the third day post-operative. His nausea and vomiting and gastric distress were successfully combated with flaxseed poultices, intravenous glucose, and gastric lavage with warm bicarbonate of soda solution. From the fourth day post-operative he felt very well. Sutures were removed on the tenth day. On the

twelfth day, X-Ray showed the gastroenterostomy to be functioning perfectly and the patient was up and about the ward. On August 30th, thirteen days post-operative he was discharged home on a Mills IV diet.

At no time during the stay in the hospital were the pulse, temperature or respirations alarming, nor did they point to any activity of a tuberculous process.

**Pathologic Examination** The lower third of the stomach was received in formol. Grossly it showed only what appeared to be an ordinary chronic gastric ulcer about 6 millimeters in diameter with considerable fibrosis extending around it and through the gastric wall. Sections cut at various levels through the ulcer showed it to be the usual type with callus extending entirely through the musculature. In addition, there was, as shown by serial sections, almost a solid ring of epithelioid and giant cell tubercles in the solitary lymph follicles surrounding the margin of the ulcer. Blocks from the gastric mucosa at a little distance from the ulcer showed fewer or no tubercles. Several small regional lymph nodes were completely filled with non-caseating miliary tubercles.

Persistent attempts to show the characteristic rods of tuberculosis by modifications of the Ziehl-Neelson staining method were futile. However, within the tubercles, and at no other place, globular and ovoid bodies, varying from one micron to four microns in diameter, and staining a bright red by the acidfast method, were shown. Some of these bodies appeared to lie extra-cellular, a few were definitely within the giant cells.

No spirochetes could be found after many attempts to stain them.

#### Case Report No 2

L. N., case no 199452, male, age 5 years, of Mexican descent was admitted to the Pediatrics service August 5, 1926, his parents complaining that he had been sweating a great deal, that he had no appetite, and that he had become very weak.

**Present Illness** The child began to lose weight five months prior to admission, grew weaker and went steadily down hill. A

month before entrance he began to cough. The cough became progressively worse. He did not complain of pain.

**Past History** Diphtheria at the age of two. No other contagious diseases.

**Family History** No tuberculosis. Venereal diseases denied.

**Feeding History** Breast fed until one year of age.

**Physical Examination** A male child, breathing rapidly with dilatation of the alae nasi, sweating about the face and apparently acutely ill. Eyes wide open with a lateral nystagmus. **Head** No abnormalities of the skull or scalp. **Eyes** Pupils equal, react to light. No conjunctivitis or keratitis. **Ears and Nose** Negative. **Mouth** One carious molar. Tonsils are of medium size, not septic. **Neck** Palpable cervical glands, not definitely enlarged. **Chest** Mild rachitic rosary present. Normal expansion on both sides. **Lungs** Marked dullness throughout the area of both lungs. Breath sounds bronchial in type. Numerous coarse râles heard throughout, the parenchyma of both lungs. **Abdomen** Prominent and rigid. No masses could be felt but there was dullness in each flank. **Extremities** Atrophy of the musculature. Edema of the ankles and feet. **Reflexes** Knee jerks present, diminished. Babinski and Chvostek's signs not present. **Impression** Miliary tuberculosis, tuberculous peritonitis.

**X-Ray Findings** Trachea, heart and mediastinum displaced to the left. Both halves of the diaphragm partially obscured. Right costophrenic angle practically obliterated. The right lung field presented a pneumothorax at the apex to about the 3rd rib anteriorly, with a caseous consolidation from the second to the sixth ribs anteriorly and mottled lung below. Left lung field was encroached upon by heart and mediastinum, that part which was free was mottled throughout.

**Urine Examination** Essentially negative, except for a few white blood cells in the sediment.

**Blood Examination** Wassermann test not done. Hemoglobin 70 per cent, red

blood cells 4,440,000, white blood cells 18,000 Differential Polymorphoneutrophils 56 per cent, small lymphocytes 20 per cent, large lymphocytes 18 per cent, transitionals 6 per cent

*Spinal Fluid Examination* Pressure normal fluid clear No increase in globulin Sugar 0.081 per cent Culture negative

*Tuberculin Test* 0.1 milligram each of old tuberculin, human and bovine, intradermally showed positive reactions at 24 and 48 hours

*Course while in Hospital* The child went steadily down hill, coughing could not be controlled by paregoric Perspired a great deal, took very little food Frequently cyanotic, respirations became more and more labored The temperature varied from 97° F to 102° F, the pulse averaged 135, respirations from 25 to 40 per minute The patient expired five days after admission

*Autopsy* was performed 12 hours post mortem The gross pathological diagnosis was as follows Advanced pulmonary tuberculosis with caseous pneumonia Active chronic caseating peritoneal tuberculosis Generalized miliary tuberculosis Tuberculous ulceration of Peyer's patches Early tuberculous leptomenigitis Chronic adhesive pleuritis Chronic adhesive perisplenitis and perihepatitis Ascites Left-sided hydrothorax Fatty infiltration of the liver Parenchymatous degeneration and acute passive congestion of all organs

The *microscopic findings* on the autopsy material which are of interest were as follows

*Brain* Congestion and oedema of meninges and brain substance No tubercles found

*Heart* Epicardium thickened Areas of epicardial adhesions Small foci of mononuclear infiltration beneath serosa, some showing caseating young miliary tubercles Atrophy of myocardium with marked subendocardial fatty degenerative infiltration Serosus atrophy of subepicardial fat

*Lungs* Acute passive congestion Numerous tubercles in all stages from young

miliary tubercles to large caseous masses of conglomerate tubercles Large parts of lung are completely replaced by caseation with very little tuberculous granulation tissue, the lung architecture being visible only in small areas In these places the picture was that of a caseous pneumonia Pleura much thickened by edematous connective tissue containing masses of caseating tubercles

*Bronchial Nodes* Completely replaced by masses of confluent caseating tubercles

*Larynx* Edematous

*Thymus* Fatty atrophy No tubercles found

*Spleen* Many large caseating tubercles, also areas of caseation without tubercle formation

*Large Intestine* Caseating tubercles, some of them confluent in the serosa and subserosa No tubercles found in the mucosa or submucosa

*Small Intestine* Large masses of caseating tubercles in subserosa, muscle coats, and submucosa Tuberculous ulceration of Peyer's patches By modifications of the Ziehl-Neelson staining method, typical tubercle bacilli were found, shaped as slightly curved rods with beading, on the mucosa, clinging to the surface of the ulcers, and within the tuberculous lesions in the depths of the tissue

*Stomach* (The gross examination of the stomach was negative) Chronic catarrhal gastritis Lymphoid tissue hyperplastic Groups of multinucleate giant cells in lymphoid tissue, representing early miliary tubercles There was no ulceration Modifications of the Ziehl-Neelson staining method failed to demonstrate typical tubercle bacilli within these lesions as rods However, acid-fast bodies identical with those found in the tubercles in Case No 1 were found in the tubercles in the submucosal lymphoid tissue of the stomach in this case Spirochetes could not be found

*Pancreas* Post mortem change Caseating tubercles in suprapancreatic lymphnodes

*Liver* Marked fatty degenerative infiltration particularly in the peripheral part of the lobule Numerous miliary tubercles, many showing caseation

*Gall Bladder* Negative

*Adrenals* Large masses of caseating tubercles in the peri-adrenal tissue, invading the adrenal cortex by direct extension. Small miliary tubercles in the substance of the adrenal.

*Kidneys* Passive congestion. Cloudy swelling. Fat dye showed no lipoidosis. Occasional miliary tubercles in the kidney substance.

*Ureter* Negative

*Retroperitoneal Lymph Nodes* Completely replaced by masses of confluent caseating tubercles.

*Testes* Edematous. Infantile.

*Urinary Bladder* Negative

### DISCUSSION

From the clinical and pathological consideration of these two cases, we deduce that the mode of infection of the stomach with tuberculosis in Case No 1 was similar to the cases described by Hurst and others—infection of a chronic gastric ulcer by tuberculous sputum (or, at least, by tuberculous material within the lumen of the stomach, whether it has entered there by means of swallowed sputum, infected milk, or anti-peristalsis from the intestines). Our reasons for believing this are

(1) The clinical history of the present illness extended over a period of ten years.

(2) The amount of scarring about the ulcer indicated that it was probably several years old.

(3) From the size, number, proportion of lymphoid, epithelioid, and reticulo-endothelial elements, and absence of caseation in the tubercles, we judge them to be fairly young. Further, from the same considerations, we

judge the tubercles within the regional lymph nodes to be younger than those in the lymph follicles immediately surrounding the ulcer.

In case No 2, with very early miliary tubercles in the submucosal lymphoid follicles, and widespread miliary tuberculosis elsewhere, it seems only reasonable to conclude that the process in the stomach is merely part of a general lymphogenous dissemination.

Heretofore, in order to establish an absolute diagnosis, it has been deemed necessary to demonstrate tubercle bacilli in the depths of the lesions. In our cases, as well as in the cases of many others with excellent histologic and presumptive evidence that the lesions were definitely tuberculous, no typical rod-shaped organisms could be shown by acid-fast stains. We believe, however, that our finding of the acid-fast bodies within the tubercles, although these bodies are of globular or ovoid form, lends support to the histologic evidence of tuberculosis. Whether these acid-fast bodies are degeneration forms of the tubercle bacillus or evidence of pleomorphism we are not certain, they may perhaps be allied to the granules described by Much. Our reasons for attaching importance to them in substantiating the histologic findings are as follows:

(1) They occur only within areas of inflammatory reaction which fit the accepted description of tubercles. They do not occur in other places in the sections.

(2) In certain places in the sections in both cases, these bodies are found

within the giant-cells, apparently having been phagocytized

(3) They do not resemble connective tissue elements which are known to retain the acid-fast stain

(4) They are not degenerating erythrocytes within capillaries or lying in the tissue,—elements which retain the acid-fast stain

(5) Identical acid-fast staining bodies can be shown on the serosal side of lesions in some cases of tuberculous entero-colitis, and what is apparently a transition from the rod-shaped organisms to the globular acid-fast forms can be traced in layers from the mucosal side toward the serosal side

In the technical work required in the preparation of these cases we experienced some of the feelings which other observers have had, when faced with the problem of establishing the diagnosis by the demonstration of the acid-fast staining rod-shaped organism, they have been unable to do so. We have a strong feeling that many of the cases which in the past have been qualified as only "probable" because nothing more than the histologic description could be given to support the diagnosis would be put on even a firmer basis if the acid-fast bodies which we have seen within the lesions in our cases had been described and recorded

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# Christian's Syndrome and Lipoid Cell Hyperplasias of the Reticulo-Endothelial System

By R S ROWLAND, M D, *Detroit, Michigan*

CHRISTIAN'S Syndrome of Defects in Membranous Bones, Exophthalmos and Diabetes Insipidus is a rare syndrome of early childhood

Recently, (*Archives of Internal Medicine*, November 1928), I discussed fourteen cases of this condition, twelve that had been reported in the literature and two new ones of my own, bringing them into relationship with several similar cases that had been recorded as a special form of xanthoma

The entire group I regarded as a generalized xanthomatosis, representing pathologic lipid storage, or lipid cell hyperplasia, of the reticulo-endothelial system

The pathologic change in these cases occurred as hyperplastic plaques and nodules arising from the areolar tissue, especially of the dura, periosteum, pleura and peritoneum and also to a less degree, as a more diffuse process, in the interstitial tissue of various organs, particularly, the liver, lungs, lymph nodes, bone marrow, spleen, glands of internal secretion and certain nerve structures

As the clinical and anatomic features of Christian's Syndrome have not been generally discussed, in this manner, up to the present time, I wish to consider these features in so far as

records permit and in so doing, give further reasons for correlating the different lipid cell hyperplasias of the reticulo-endothelial system, which this unique syndrome suggests

Considered in all its many forms lipid cell hyperplasia of the reticulo-endothelial system cannot be regarded as a rare condition and this remarkable pathologic storage of lipoids in the body presents so many problems of general medical interest, it should be better known

H A Christian, in 1919, first drew attention to this unique syndrome under the title "Defects in Membranous Bones, Exophthalmos and Diabetes Insipidus, an Unusual Syndrome of Dyspituitarism," reporting a case presenting this symptom complex and citing two similar cases previously described by Schüller Hand, in 1921, discussed three more cases, including one previously reported by Kay Since then Grosh and Stifel, Thompson Keegan and Dunn, Danzer, and Kyrklund have each reported one case Recently I have added two more cases of my own to this list

Three cases recorded in the dermatological literature, which resemble this syndrome, were reported by Pusey and Johnstone Spillman and Watrin, and Weidman and Freeman I wish, especially, to draw attention to the lat-



polyuria and thirst suddenly developed. He passed 27 quarts of urine daily. He was much undersized for his age. It was observed that his breathing was stertorous. The bones were normal except for very extensive cranial defects and similar changes in the maxillae. Kay evidently thought that the condition was due to a tumor at the base of the brain.

Hand's third case was in a boy, aged 4 years, who had had a tumor-like swelling removed from the left parietal region at the age of 2 years. There had been an absence of bone at this point, the mass seeming to arise from the dura. The pathologic report of the tissue removed was "No gumma, no sarcoma, slight degree of inflammation, mainly a myxomatous change." Since then other swellings had appeared and exophthalmos, greater on the left side, had developed. In this report Hand stated that "no polyuria has developed as yet." The x-ray showed marked cranial defects, but "no involvement of the sella turcica," and "so no symptoms of diabetes insipidus."

Grosh and Stifel's patient, a girl, aged 7 years, was weak and did not develop from the second year. She was markedly underweight and underheight. At 6 years she began having trouble with her teeth and with the left mastoid, which was opened and drained. Her mouth became sore with a bullous eruption on the gums, which necessitated the removal of some of the unerupted permanent teeth. Seven weeks after the operation on the mastoid she suddenly developed polyuria and thirst. Examination at 7 years showed a bad condition of the teeth

and gums, extensive cranial defects, dwarfism, typical diabetes insipidus and unilateral exophthalmos. There were similar bony defects of the maxillae and left ilium. When she was observed three years later, there was hardly any increase in her size, no obesity and the genitals were normal. The left ear was still discharging. The cranial defects had increased slightly. There was no x-ray evidence of involvement of the sella turcica.

Thompson, Keegan and Dunn's patient was a pale, poorly nourished boy of 9 years. At the age of 7½ years, he had a severe attack of measles. Following this, he was in a weakened condition and the gums became sore and the teeth loosened. Six months after the measles, excessive thirst and polyuria suddenly developed, persisted for a few days and then disappeared. At this time, soft spots on the right side of the head were observed. A year after he had had the measles, polyuria and thirst again appeared. The boy was emaciated, with a sallow skin. There was moderate exophthalmos, marked gingivitis and clean and sound but loose teeth. The x-ray showed extensive bony defects of the skull, described as "geographical skull." The sella turcica appeared normal, but there were extensive similar defects in the maxillae, pelvic bones, upper portion of the right femur and ribs. The body of the fourth lumbar vertebra was collapsed. A tentative diagnosis of multiple myeloma was made. This patient was under observation about eighteen months, during which time he grew progressively worse. He became pale and emaciated, suffered from backache and pain in the left hip and

walked with a marked limp, listing forward to the left. Exophthalmos was marked. The entire skull was soft and doughy, with only an irregular framework of supporting bony ridges. The gingivitis was severe, and the teeth were held by soft investing tissue as the alveolar processes had been absorbed. An x-ray of the chest revealed a diffuse increase in density, characteristic of chronic interstitial pulmonitis. As death approached, the cough and dyspnea became more troublesome. The end came suddenly, and was attributed to impaired circulation incident to intense pulmonary fibrosis. At autopsy, the scalp showed fibrous adhesions. The inner surface of the dura was mottled by dull yellowish white tissue, which took Sharlach R fat stain. The large yellow infundibulum stalk was fibrosed. There was involvement of the middle ear and of the petrous portion of the mastoid. The ethmoid cells were obliterated by the same tissue growth. The pathologic diagnosis in the case was "exophthalmos, decalcification of bones, fibrosis of the tuber cinereum, slight subacute inflammation of the pars posterior of the pituitary gland, chronic interstitial fibrosis of the lungs, hypertrophy of the heart, chronic passive congestion of the liver and spleen, hypertrophy of the kidneys and bladder." From their histologic study, Thompson, Keegan and Dunn considered the condition "inflammatory, rather than degenerative or a primary metabolic (endocrinologic) process."

Danzer's patient was a boy, aged 4 1/2 years, who had recently had his tonsils removed. He was miserable,

having had repeated attacks of sore throat. Two months after the operation, his mother first noticed soft tender spots on his head. He was pale and stoop-shouldered, with exophthalmos, bad teeth, spongy gums and many soft spots on his head. He complained of thirst and polyuria, which had evidently developed suddenly a year after the soft spots were first observed. The x-ray showed extensive cranial defects and similar changes in the maxillae. Danzer makes no comment regarding the bones of the rest of the body and does not discuss the etiology.

Kyrklund, under the title "Thinness of the Skull, Exophthalmos, Dystrophia Adiposogenitalis and Diabetes Insipidus," reports a case. His patient, a girl, aged 12 years, was normal up to the age of 2 years, at which time she developed a cough, began breathing rapidly and became emaciated. At 4 years she developed thirst and polyuria. At the age of 7, she suddenly became fat, walked stiffly and complained of pain in the legs. The skin of the head was so tender that she could not stand having her hair combed. Growth was noticeably retarded, as was mental development. She was dyspneic. Her lips, hands and feet were cyanotic. She had the typical appearance of dystrophia adiposogenitalis. Examination showed that there were numerous cranial defects. The long bones were normal. The teeth were in a bad condition and exophthalmos was present. At autopsy, the scalp was adherent to the calvarium around the soft areas and when separated, yellow detritus-like material flowed out leaving cyst-like depress-

sions The inner table in these places was eroded and the space filled with brownish yellow tissue arising from the dura. The dura had grown firmly to the inner table and showed yellowish brown, tumor-like thickenings. The region of the hypophysis did not show macroscopic changes, but there were growths in the brain stem behind the hypophysis of the same brownish yellow color. There were extensive changes in both lungs and pleura. "The structure of the lesions, on the whole, was similarly formed of connective tissue cells, part round cells, and some spindle cells. Lesions in the brain stem contained irregularly formed giant cells. The histological process did not simulate tuberculosis." Kyrklund considered the "condition due to a tumor of sarcomatous nature," and believed the "diabetes insipidus secondary to the growth in the region of the hypophysis."

Milne's patient was a quarter-cast Maori boy, aged 3 years, who had been suffering from three months from loss of appetite, polydipsia and polyuria, together with exophthalmos, particularly on the right side. He had an extensive discrete papular eruption on the chest and back, many of the papules being surmounted by small oval crusts of seborrheic appearance, which, in certain parts, appeared infected and erythematous. The child was peevish and puny, although of normal mentality. The skull on x-ray examination presented many deficiencies in the cranium. In plates taken 9 months afterwards, the skull defects appeared smaller. His last weeks were marked by an irregular temperature and troublesome bronchitis. Autopsy On

reflecting the scalp, a number of swellings resembling putty in appearance, but of fairly firm consistency, were observed. These areas were extensions, through small perforations in the skull, from the dura which was extensively infiltrated. The brain was normal. A compact yellow mass about the size of a walnut rose up out of the sella turcica, displacing the hypophysis, but without eroding or distorting the clinoid processes. Another mass projected back from the right wing of the sphenoid. It also extended to the ethmoid and both orbits. The histological description of this tissue was "Striking yellow mass—composed of spindle cells with large clear spaces filled with granular yellow substance. Scattered throughout the tumor were giant cells with rosette nucleus surrounded by a granular zone. The nodules from the dura showed the same changes. The entire pituitary was invaded by the yellow growth." Milne regarded the condition due to a tumor arising in the hypophysis. No report was made of the rest of the body.

(Author's cases recorded in full in the Arch of Int Med, Nov 1928)

My first patient was a boy 5 years old, who was normal and healthy until 2 years of age when, following an attack of measles, he did not seem as well as usual. Six months later a swelling and tender area appeared on his head, ascribed to a fall. When 3½ years old, another swelling appeared. Examination at that time showed a poorly nourished boy with numerous cranial defects, loose teeth, swollen and tender gums and marked exophthalmos. There were no urinary symp-

toms I first saw him eighteen months later, because of shortness of breath and a difficulty in walking which had increased rapidly during the past three months. He had the bend-over, dwarfish, frog-like appearance described by Hand. There was a slight purulent discharge from both ears. The alveolar arches were swollen and tender, and only three very loose teeth remained in a swollen tender jaw. His skin was not especially dry and he did not show any eruption. There was a slight yellow tint to the skin. He was somewhat cyanotic. Roentgen ray examination showed multiple cranial defects involving the vortex and base of the skull, with very extensive erosion of both upper and lower jaw bones, and a slight defect in the right ilium. The urine was negative. Blood showed hemoglobin, 57 per cent, red blood cells, 4,150,000, white blood cells, 17,350. Differential polymorphonuclears, 64 per cent, large mononuclears, 32 per cent, small lymphocytes, 4 per cent. Intradermal tuberculin test was negative. Wassermann reaction negative. The patient grew progressively weaker. His death was attributed to cardiac failure due to impaired circulation resulting from extensive pulmonary fibrosis. Autopsy revealed extreme pallor of the skin and marked exophthalmos. When the calvarium was exposed there were numerous annular defects of the cranial bones. These defects were filled in with a gummy semicaseous, bright yellow tissue of rubbery consistency. On removal of the skull cap, it was found that the tissue could be easily pushed out of the defects, leaving ragged holes in the skull. This tissue ap-

peared to arise from, and be continuous with, the dura. The brain was edematous, but otherwise normal. The base of the skull was covered with plaques of the same yellow granulomatous-like tissue which extended forward into both orbits and completely surrounded the region of the hypophysis. In this region there was extensive bone destruction. There was a marked atrophic process of both middle ears, without destruction of bone. The heart was markedly enlarged. The lungs were voluminous and felt fibrous to palpation. They were adherent in the posterior lateral aspect, with adhesions of the same gummy yellow tissue noted in the granulomas of the dura. On section, the whole lung was a mass of communicating vesicular cavities, varying from the size of a pinhead to that of a pea. The septum between the cavities was fibrous and inelastic. When the ilia were exposed there was found in the eroded area of the right ilium a yellow plaque about 1 cm in diameter, with a bone defect of the same character as seen in the skull. A similar yellow plaque 2 cm in diameter protruded from the periosteum on the right side of the body of the first lumbar vertebra. The dural plaques consisted of masses of lipoid-containing cells of reticulo-endothelial type resembling xanthoma. Throughout were numerous multinuclear giant cells. In the old tissue of the dura were numerous small calcareous concretions. In lipoid masses were areas of cholesterol crystal formation, with cholesterol clefts and with many multinuclear giant cells. Giant cells, evidently foreign body giant cells, surrounded the cholesterol crys-

tals. These plaques did not suggest infectious granuloma but resembled xanthoma or masses of cells of the xanthoma type, and probably consisted of proliferated reticulo-endothelial cells with cholesterolosis. Fat stain showed cells to be loaded with lipoids. Chronic bronchopneumonia, with localized patches of fibrosis and alternating patches of emphysema, was found in the lungs. The reticulo-endothelial cells around the pulmonary vessels showed the same hyperplasia and lipoidosis seen elsewhere, and projecting into the larger bronchi were papillary overgrowths of fibroblastic tissue and reticulo-endothelial tissue showing lipoidosis. The pleura was thickened with reticulo-endothelial hyperplasia and lipoidosis. The liver presented marked passive congestion. The lipoidosis was slight in the liver cells, more marked in the periphery of the lobules, and there was some atrophy of the cells. Many lipid Kupffer cells were found. The lymph nodes showed lymphoid exhaustion of the germ centers. Proliferation of the reticulo-endothelium with lipoidosis and slight pigmentation was present. The proliferation of the reticulo-endothelium and lipoidosis varied greatly in the different nodes, being quite marked in some, while others showed them to a slight degree. All through the retroperitoneal tissue there were bands of the atypical tissue. The bones showed atypical marrow. There was reticulo-endothelial hyperplasia with many multinuclear giant cells and many lipid cells. Rarefaction of the bony trabeculae was found. (The bone absorption resembled that seen in some cases of osteomalacia.) The

muscle fibers of the heart were fairly well developed for this age. Little lipoidosis of the muscle and no reticulo-endothelial proliferation and no lipoidosis in the stroma were found. The testes were apparently normal for the age. Lipoid cells were not found in the testes or epididymis. The kidneys were congested with edema and some lipoidosis of the renal epithelium. Small concretions of lime salt were found in some of the tubules. Proliferation of the reticulo-endothelium and lipoidosis were not found. Sections from the brain did not show any pathologic change except slight edema. The thyroid gland showed a colloid content normal for this age, with undeveloped adenomatous tissue. Throughout the gland, there were a number of sharply circumscribed areas of proliferation of the stroma having an epithelial appearance in the center, with some lipoidosis. The suprarenals showed hypoplasia which was especially marked in the medulla. Moderate lipoidosis of the cortical cells was present. In the perisuprarenal tissue there were small areas of proliferating reticulo-endothelium. The large epithelioid cells showed more lipoidosis and some pigmentation, thus resembling xanthoma cells. In one section in the medulla were small areas of proliferating reticulo-endothelial cells with lymphocytic infiltration. The pineal gland was edematous and congested. Lime salt deposits or lipid cells were not present.

The clinical diagnosis was membranous bone defects, exophthalmos and dwarfism—Christian's syndrome. Generalized xanthomatosis of a visceral type was found. The condition was

regarded as a particular juvenile form of lipoid cells hyperplasia of the reticulo-endothelial system

My second patient was a boy, 3 years and 11 months old, who developed normally during the first year. When he was slightly under 2 years, he became irritable, complained of a sore mouth, began to ask for water frequently and pass large amounts of urine. The soreness of the mouth grew worse and several of the back molar teeth loosened and came out. The symptoms of thirst and polyuria were variable. He was treated in the Children's Hospital several months. During this time bone defects were discovered in the skull. There was also involvement of the fifth rib and an area of decreased density in the right ilium. There was some unexplained irregularity in the temperature and his weight fluctuated considerably. When I first saw him 14 months later, his appetite and digestion were good. He complained of only moderate thirst and passed from 6 to 8 quarts of urine in 24 hours. His mother first noticed, at this time, that he had not grown. Examination showed bone defects of the cranium, slight exophthalmos of the left eye, swollen and tender gums. All the molar teeth in both upper and lower jaw were loose. The teeth, themselves, were in a good condition. Roentgen ray examination revealed marked extension of the bone erosion in the skull bones and maxillae and changes in the 5th rib. This patient has been under observation for nearly 3 years. He appears well, has a good color, his polydipsia and polyuria cause little disturbance, more surprising, the bone

defects cannot be felt on palpation and he made a fair growth during the time he was under treatment. The roentgen ray examination shows almost complete closing in of the bone defects.

The clinical diagnosis was Christian's syndrome of membranous bone defects, exophthalmos and diabetes insipidus. The condition was regarded as generalized xanthomatosis, a juvenile form of lipoid cell hyperplasia of the reticulo-endothelial system.

Griffith's patient, a much undersized boy of 9 years, had been healthy and normal up to 2 years. At the age of 2½ years, he had pertussis. At 3 years he had a temporary enlargement of the abdomen and "yellowness." Growth was evidently retarded from this time. At 8 years he had another attack of jaundice and swellings on the head following contusion, and an eruption appeared all over the body. The child was undernourished and underdeveloped, with extensive cutaneous xanthoma eruption, evident exophthalmos, marked irregularities of the teeth, defects in the skull and typical diabetes insipidus. The liver was felt 3 cm below the costal margin, the spleen felt 4 cm below the costal margin. The post mortem study of this case was made by Weidman and Freeman. The liver was enlarged, slaty green and had the appearance of hypertrophic biliary cirrhosis. There was extensive lipoidosis and fibrosis. The lungs showed the same changes with more fibrosis and localized areas of round cells and some lipoidosis. The cut section of the lungs showed marked fibrosis together with emphysema, yellow mottling could be made out on the cut surfaces. The peribronchial lymph

nodes showed varying amounts of lipoidosis, fibrosis and round cell infiltration. The pituitary was large, firm and bright yellow. In the brain tissue, in this region, there was yellowish lipoid infiltration. This appeared to extend from the meninges inward. The posterior lobe of the pituitary was completely fibrosed, with some lipoidosis; the anterior lobe was found normal. The pineal gland was involved. In the brain, it was thought that the lipoidosis concerned the glia cells. The authors state that many of the organs reflected the general sclerosing effect of a person dying of senility. There were fibrous nodules, also, on the margin of the mitral and tricuspid valves. The spleen was very large and slightly fibrosed. The kidneys showed passive congestion. Suprarenals were small, thin, flat, and reduced in lipoid content. The pancreas was hypertrophic. Weidman and Freeman regarded the condition as a general systemic chronic inflammatory process, resulting either from a metabolic dyscrasia, producing abnormal metabolites or a low grade infection similar to tuberculosis and syphilis.

Berkheiser reported a case under the title "Multiple Myeloma of Children," which appears to belong in the group I am describing. Berkheiser's patient was a girl, aged  $3\frac{1}{2}$  years. She had had a normal first year, except for a mild attack of measles at 9 months. Then she developed a severe eczema about the head, which spread to the body. Exophthalmos was first observed when she was 16 months old. Later she complained of pain in the right leg, hip and arm, and had difficulty in walking. She was irritable,

had a slight elevation of temperature and gave a history of bed wetting. Examination showed an undernourished, undersized child, with marked exophthalmos and eczema of the scalp. The cervical, axillary and inguinal glands were pea to marble size. The liver and spleen were palpable. There was tenderness over the right inguinal region and posterior to the upper end of the femur. The x-ray revealed extensive bony defects of the cranium, the pelvis, the upper portion of the right femur and the lower portion of the left humerus. Blood hemoglobin, 44 per cent; red blood cells, 3,500,000; white blood cells, 7,000. Wassermann reaction negative. Urine negative. Biopsy was taken from the skull and right humerus. Tissue was reddish in its peripheral portion, but yellowish in its inner portion, where it had broken down and formed a cyst. Microscopic examination of the soft tissue showed many spherical reticular cells and spindle shaped fibroblasts, many giant cells of foreign body type. In the part away from the periphery were numerous large vacuolated cells, many of them mononuclear but also many of them polynuclear, typical xanthoma cells. The mass was also filled with blood cells, myeloblasts, myelocytes and eosinophiles, blood vessels were numerous. Sections from the skull showed similar changes. Berkheiser's diagnosis in this case was xanthomyelomata.

Schultz, Werbster and Puhl's patient was an undersized, poorly nourished girl,  $2\frac{1}{2}$  years of age. She had a normal birth and was breast fed. She had swollen glands and eczema at 9 months, regarded as scrofula. Her

weight varied greatly, at no time was it normal. When 2 years of age, following measles, she complained of pain in the left temporal region and neck. A yellow swelling appeared on the forehead which was opened and drained. It healed slowly with the formation of a yellow crust. Examination at 2½ years showed an emaciated child, small for her age, with a pale, straw yellow colored skin. There were extensive bone defects of the skull involving, especially, the temporal region, a surprising exophthalmos and enlargement of the cervical glands. Her spleen, the size of a hand, protruded to the level of the umbilicus and the liver was also markedly enlarged. The urine was negative, but the blood showed an extreme degree of anemia—a picture of anemia pseudoleukemia infantum. Blood 5-20-23. Hemoglobin, (Sahli) 26 per cent, red blood cells, 1,210,000; white blood cells, 6,900. Differential polymorphonuclears, 67 per cent, large mononuclears, 4%, small lymphocytes, 26%, myelocytes, 1%, basophiles, 1%. 6-6-23. Hemoglobin (Sahli), 17 per cent, red blood cells, 1,250,000, white blood cells, 9,100. Differential polymorphonuclears, 58 per cent, large mononuclears, 5 per cent, small lymphocytes, 28 per cent; eosinophiles, .5 per cent. Poikilocytosis, anisocytosis, polychromatophilia, 8 normoblasts and megaloblasts in a count of 200 leukocytes. 6-14-23. Hemoglobin (Sahli), 14 per cent, red blood cells, 980,000, white blood cells, 17,800. Differential, polymorphonuclears, 50 per cent; large mononuclears, 7 per cent; small lymphocytes, 36 per cent, young forms, 5 per cent. High grade poikilocytosis,

anisocytosis, polychromatophilia, 21 normoblasts in a count of 100 leukocytes. Autopsy showed the following bone defects of the skull in the frontal and occipital region and very extensive at the base of the skull. A large part of the orbits were transformed into hard fibrous pigmented tissue. The pia mater was thickened. Brain normal. Lungs unusually firm showing grayish yellow nodules. Bronchial and tracheal lymph nodes enlarged. Spleen very large with thickened fibrous capsule. On section, there were many corn size, whitish nodules and some infarct-like lesions near the surface. Pancreas usual size and firm. Liver very large, pale brown, with many scattered grayish nodules like those in the spleen. Peyer's patches swollen. In many parts of the skeleton irregular yellowish white areas were found in the spongiosa. Schultz, Wernbter and Puhl considered the condition a disease of the reticulo-endothelial system and supposed an infection of unknown type to be responsible.

Herzenberg's patient was a girl, aged 5 years, who had always been normal and had had no illnesses, with the exception of measles and pertussis, up to 3 years and 10 months, when she developed a diabetes insipidus, which receded in the course of a year. Later she began to have fever, pains in the head, arms, ribs and legs, and developed a high degree of anemia. Blood 1-16-26. Hemoglobin, 70 per cent, red blood cells, 4,760,000, white blood cells, 8,800, lymphocytes, 62.5 per cent. 1-11-27. Hemoglobin, 29 per cent; red blood cells, 3,585,500, white blood cells, 11,900, lymphocytes 50



per cent 12-19-27 Hemoglobin, 9 per cent, red blood cells, 1,030,000; white blood cells, 10,000, lymphocytes, 45 per cent. Platelet count, 22,660 5 normoblasts in a count of 200 leucocytes, poikilocytosis, anisocytosis, and polychromatophilia 1-7-28 Hemoglobin, 78 per cent, red blood cells, 740,000, white blood cells, 11,000; lymphocytes, 71 per cent. Many normoblasts and megaloblasts A papulous skin eruption appeared on various parts of the body The superficial lymph nodes were enlarged, and during observation, the liver and spleen became palpable She was very irritable, the itchy papulo-pustular eruption increased, there was edema of the face, hands and feet, the temperature fluctuated Autopsy revealed a well built, but emaciated child, with a pale, slightly yellow skin and an extensive roseola, papular exanthem of the face and trunk On the forehead were greenish yellow purulent crusts The cervical, axillary and inguinal lymph nodes were enlarged and on section yellowish red The surface of the cranium was covered with small light yellow spots giving a mottled appearance There were numerous bone erosions, in some places, limited to the lamina externa, and in other extending through the diploë and lamina interna, or, limited to the lamina interna These defects were filled with yellow to dark yellow masses of a soft rubbery consistency There were larger areas of bone destruction at the base of the skull In both fossae were yellowish red masses Similar masses spread over healthy bone, surrounded the thickened infundibulum and extended into the sphenoidal and eth-

moidal sinuses There was no extension into the orbits and no bone erosion about the orbits The middle ears were filled with a yellow viscid material On both the inner and outer surfaces of the dura were deep yellow circumscribed map-like deposits, which, in some places, thickened to tumor-like proportions Here and there, especially on the inner surface, these masses appeared to have a fine hemorrhagic covering In place of the thymus, there was a dark yellow tumor mass containing fat-like tissue The heart muscle was fatty spotted In the aorta there were yellow plaques In the tonsils there were hazel-nut sized yellow masses The gastric mucosa was yellowish with lighter spots. Liver slightly enlarged Under the serosa and on section, near the surface, many dark yellow red bordered nodules were visible. The suprarenals were of normal size, the cortex thin and dark yellow The spleen was somewhat enlarged and on section there were many grayish yellow, irregularly formed lentil sized areas In the inner part of the pulp there was a group of yellowish gray areas the size of a cherry cluster Some of the intraabdominal and periportal lymph nodes were enlarged to hazel-nut size Those in the mesentery were yellow to yellowish red on section The bone marrow of the ribs and sternum was dark red, that of the vertebra was dark red with a yellowish ground There were grayish yellow spots in the marrow, especially in the long bones Anatomical diagnosis. Niemann-Pick's disease Splenohepatomegaly Lipoid cell hyperplasia of the intraabdominal organs, extra and intrathoracic lymph nodes.

Lipoid cell infiltration of the dura mater and skull bones Hemorrhagic diathesis Anemia Histological findings Lipoid cell infiltration of the skull bones and dura mater Lipoid cell hyperplasia of all the various infected organs, principally of the skeleton and other organs, which macroscopically appeared unchanged Pronounced fibrous change in lipoid-containing tissues in the spleen, and especially the femur and skull bones (Herzenberg considered her case as representing a skeletal form of Niemann-Pick disease)

#### GENERAL CONSIDERATION

*Clinical and Symptomological* The seventeen cases I have cited as representing Christian's syndrome were in young children Eight of the patients were girls and nine were boys

The family histories, in my original group, as far as they were known, did not show any unusual features, with the exception of my own second case, in which a brother had hypercholesterinemia and chronic valvular disease without a rheumatic history, and the mother had hypercholesterinemia and a sallow complexion But Herzenberg in her recent paper, gives an account of a sister of her patient who had a bronzing of the skin, xanthoma eruption, palpable liver and spleen, and bone defects

The obstetrical histories were normal and the births uneventful with one exception

In eleven instances the first manifestations of the disease were during the second year of life, with two in the third year, one in the fourth year, two in the sixth year and one in the

seventh Without exception, there was good health and normal development up to the time of the onset which usually occurred, following one of the common contagious diseases—measles, mumps, whooping cough or scarlet fever In the course of a few months there was increased irritability, and then either polydipsia and polyuria developed, the gums became swollen and teeth loose, the eyes became prominent or there was a discharging ear which did not respond to treatment

The progress of the disease was slow at first with remissions, and in milder cases there was very little discomfort, except from thirst and sore gums As the disease progressed, however, there was increasing irritability, sometimes a low grade unexplained temperature, as well as pain and tenderness in the head, and less often, in the neck, chest, arms and legs Examination showed the pain to be related to striking bone defects which occurred, particularly, in the flat bones of the skull The roentgen ray revealed similar, though less extensive, defects in the maxillae, and the flat bones of the pelvis, rarely the scapulae, vertebrae and ribs Sometimes, the long bones—femur and humerus—had the same bone deficiencies These areas of bone rarefaction appeared to increase rapidly during the active stage of the disease, but when the condition was inactive, there was an arrest, or, in cases that improved, there was, in the roentgen ray picture, the appearance of a receding of the bone defects

In the same way the diabetes insipidus sometimes developed suddenly, then gradually subsided or stopped, to appear again later, and the exophthal-

mos varied in degree. In none of the cases was there any evidence of increased intracranial pressure.

For a long time the nutrition was good. Frequently, there was a lemon yellow tint to the skin, sometimes mistaken for jaundice, and a typical xanthoma eruption of the rapidly developing type appeared. The lesions were usually small, scattered irregularly over the face and trunk, papular, with red borders and a yellow center, giving a pustular appearance like the lesions in xanthoma diabeticorum or the rapidly developing congenital type of xanthoma.

Griffith's patient had larger skin lesions, more symmetrically arranged, typical of xanthoma multiplex. It is also of interest that Schuller and Kyrklund described fatty tumors, and Griffith's patient had larger lesions in association with the skin lesions which were probably xanthomyelomata of the tendon sheaths.

In the severer cases, as the disease progressed, it was observed that these children did not grow in a normal manner. They became stunted and emaciated. As a result of the bone defects, deformities arose, and walking became difficult. The spleen, liver and superficial lymph glands were enlarged. Anemia developed to an extreme degree, or there was increasing dyspnea and cyanosis. Death resulted in this severer form in from 2 to 4 years.

The milder cases progressed more slowly. A marked dwarfism became apparent and in two instances, (Schuller's and Kyrklund's patients), in which the affection had extended beyond the seventh year, a typical dys-

trophia adiposogenitalis developed. In one case, (Pusey and Johnstone's), obstructive growth appeared in the larynx and finally, following intubation and later tracheotomy, death resulted from intercurrent infection, at the age of 18 years.

*Laboratory findings and special examinations.* The urine was normal, except for the variations that usually occur in diabetes insipidus.

The blood changes were fairly definite. In the early stage of the disease there was only a slight degree of anemia with a moderate increase in leukocytes, this increase sometimes being due to a large mononuclear excess. In the advanced stage of the disease a severe rapidly progressive anemia often developed. The hemoglobin and erythrocytes sank rapidly to the lowest level. There was a moderate white cell increase in lymphocytes, poikilocytosis, anisocytosis, polychromatophilia and many normoblasts and megaloblasts. The blood chemistry tests were all normal, except for an increase in blood cholesterol, lecithin and total fats, in several of the cases examined. Blood and spinal fluid Wassermann and tuberculin tests were always negative.

*Anatomical and histological.* The autopsy examinations revealed bone defects preponderating in the skull, but occurring in all parts of the skeleton, and yellow to dark yellow, sometimes brown, rubbery tissue masses arising from the dura, periosteum, pleura and peritoneum. These masses were usually only slightly raised, but sometimes they assumed tumor-like proportions. In the cranial cavity where this proc-

ess was most marked, the tissue growth often surrounded, and appeared to raise the hypophysis up out of the sella turcica, it also extended forward into the orbits, nasal sinuses and middle ear and filled in the bone deficiencies. In Herzenberg's case these masses appeared to arise from both the inner and outer surfaces of the dura and calvarium, but in most instances they were found only on the outside of the dura, and also arising from the periosteum, pleura and peritoneum. In the older and more advanced lesions these rubbery, yellow masses were changed to firm, fibrous, pigmented tissue resembling scar tissue. In places there were cyst-like formations associated with this growth. Many of the organs had the same yellow color. The bone marrow of the long bones, as well as of the flat bones, usually showed changes. Sometimes there was only a darker yellowish tinting, or, there was a grayish to yellow spotting, pin point to barley grain in size. The bone trabeculae were eroded, and in places the erosion extended through the bone, causing large irregular bone defects. In some instances, the hypophysis and neighboring regions of the brain showed the same yellow change. In one case, the hypophysis was entirely sclerosed. The change also occurred extensively in the pleural and abdominal cavities. In both locations there were swollen, yellow tinted lymph nodes, and about the hilus of the spleen, liver and kidneys large yellow masses, of the same appearance, occurred. Frequently, the lungs were unusually firm and showed yellow spotting and extensive fibrosis. When the spleen and liver were en-

larged they showed the same change in color and irregular grayish white to yellow accumulations, sometimes cherry size, appeared. Occasionally, the thymus was entirely replaced by such fatty masses. Yellow masses also occurred in the tonsils, esophagus, stomach walls and Peyer's patches. The pancreas was either increased in size or unusually small and fibrosed. The suprarenals were frequently smaller than normal with a decrease in lipid content. Yellow plaques appeared in the large vessels and on the heart valves. The heart muscle was sometimes yellow spotted. The older lesions in the organs showed the same fibrous change, as in the advanced lesions, at the base of the brain. This was particularly so in the lungs. The lesions in the skin also showed the same yellow appearance, and sometimes fibrotic changes, as seen in the inner organs.

The histological examination showed many lipid-containing cells in the early rapidly developing lesions, and lipid cell hyperplasia of all the infected organs. Lipid cell infiltration of the skull bones and dura, and lipid cell hyperplasia were also found in organs which macroscopically appeared normal. There was a pronounced fibrous change in the lipid-containing tissues in the older plaques and tumor-like masses, as well as in the organs—lungs, liver, spleen, lymph nodes, bone marrow, all the glands of internal secretion, the skin lesions and parts of the central nervous system.

Microchemical and chemical analysis showed these cells to contain various lipoids—phosphatid lipid, cholest-

terol and its ester and neutral fats, in varying proportions and amounts.

All the organs participated in this change, if only to a slight degree, the preponderance of change being in the skeletal system, but the severity of the involvement of the different organs varied in each individual case and was not as Herzenberg indicates special to the spleen and liver, for in several instances, the lungs showed the most advanced change and the spleen and liver were only slightly affected.

These changes occurred in the reticulo-endothelial cells of the various tissues and organs involved, and in the advanced stages even extended over into the parenchyma of certain organs, especially of the lung, liver, spleen, kidneys and nervous system.

#### SUMMARY

This syndrome presents such a definite clinical and anatomical picture that it seems justifiable to regard these cases as all representing the same condition.

The outstanding clinical features are the very extensive large irregular, sharply outlined defects in the bones of the skull with similar, though smaller and less numerous, defects in other bones, the frequent occurrence of diabetes insipidus, exophthalmos and persistently discharging ears; the color of the skin, a characteristic skin eruption, sometimes, enlargement of the spleen, liver and lymph glands, a severe progressive anemia or bronchial symptoms with cyanosis and dyspnea, a retarded growth and the occurrence of dystrophia adipositis genitalis.

The anatomical findings which explain the symptoms are yellow to yel-

lowish brown growths arising from the dura, periosteum, pleura and peritoneum, at times assuming tumor-like proportions; a more diffuse process of the same appearance involving many organs—lungs, spleen, liver, lymph nodes, glands of internal secretion, and parts of the central nervous system and skin, lesions composed of darkly staining nuclei, of reticulo-endothelial origin, frequently, true foreign body giant cells with non-foamy protoplasm, the presence of various lipoids in the foamy cells, fibrous change in the older lesions with almost complete absence of foamy cells, round cell and eosinophile infiltration and other differences depending on the location of the lesions; rarely necrosis and cyst formation.

#### ETIOLOGY AND PATHOGENESIS

We are dealing with a slowly progressive, general disease, showing familial tendencies, which has periods of remission, but eventually overwhelms the vital organs and brings on death, although sometimes, its course is shortened by an intercurrent affection.

Various theories have been advanced as to the etiology of this syndrome. Pituitary dysfunction was first suggested because of the retardation in growth and the frequent occurrence of diabetes insipidus. One of the most interesting features in this group of cases is the constant and extensive involvement of all the ductless glands.

Naturally, the striking symptom of bone defects has attracted attention, suggesting a variety of conditions causing bone erosion. In a certain stage, this condition might be mistaken for syphilis with its enlargement of

the spleen, liver and lymph glands, but the bone defects are much more extensive and do not resemble the breaking down of a gumma with its resulting scar formation. Also, the many blood tests have been negative for lues and the lesions have not shown suggestive pathology.

Bone destruction in this syndrome appears to arise from hyperplastic areas within the bone marrow, first invading the bone trabeculae and then extending through to the outside. In the skull this may involve either the inner or outer table or include both tables, producing the large defects. The roentgen ray picture also gives this impression. The plaques arising from the dura and periosteum may or may not take part in this change, but in their growth extend to fill in the space formed by the erosion. As the hyperplastic masses in the bone marrow frequently contain many true foreign body giant cells, in my previous paper I suggested that they might be the cause of the bone erosion.

Tuberculosis might be suspected from the occurrence of bone changes and the anatomical appearance of the lesions, but tuberculin skin tests have always been negative and in only one instance was there any family history of tuberculosis. The lesions may show certain resemblances to those of tuberculosis, but they never contain Langerhan's cells, being accumulations of hyperplastic cells filled with lipoids and foreign body giant cells. I might say, parenthetically, that my conception of this disease is such that either tuberculosis, syphilis or a metastatic tumor might be complicated by this change.

In the majority of instances, the cases in this syndrome were regarded as some form of malignant tumor eroding bone—either sarcoma or multiple myeloma. In such conditions, the bone erosions are, frequently, quite as extensive, but the individual lesions are smaller and not so irregular in shape, and the pathology is entirely different.

In the rare cases of leukemia which sometimes are complicated by bone changes, this change is not nearly as extensive and the blood gives a different picture.

Occasionally, because of the massive lesions, an infectious etiology of some unknown form has been thought to be the probable cause of the disease. Schultz, Wermbter and Puhl, in their carefully studied case, considered the process a granuloma of a specific inflammation, partly, because of the fibrosis, areas of necrosis, and the presence of eosinophile leukocytes in the lesions. They believed that they were dealing with a hyperplasia of the reticulo-endothelial apparatus and that a chronic infection was responsible for the marked hyperplasia. But the extent and distribution of the lesions would seem to indicate that this is not an inflammatory hyperplasia. Furthermore, the extensive fibrosis, the rare areas of necrosis, the cyst formation, the round cell and eosinophile infiltration were only found in the older lesions and occurred in the course of their evolution, as secondary changes.

Usually, the massive portion of this infiltration arising from the areolar tissue, particularly the nodular lesions, have been separated as different from the diffuse process in the organs and

various explanations have been given for their occurrence. They have been regarded as tumors of the connective tissue secondarily infiltrated with lipoids; as special tumors developing from xanthoma cells; as granulomas developing from an inflammation of undetermined nature which had provoked a local fixation of the excess lipoids circulating in the blood; or, as granulomas that had become xanthelasmic as the result of a degenerative process which had liberated the constitutional lipid locally. In my recent paper in the "Archives of Internal Medicine," I reviewed the literature and presented reasons for regarding this group of cases as a form of massive xanthomatosis, as it frequently occurs in early childhood. This condition representing lipid cell hyperplasia of the reticulo-endothelial system and the pathologic change, diffuse and nodular, being the manifestation of a primary disturbance of the lipid metabolism.

Local liberation of lipid may cause the formation of cholesterol granulomas. Various inflammatory and suppurative processes, as well as mesenchymal tumors, can be complicated by lipid infiltration. Because of the extent and similarity of the lesions found in Christian's syndrome, I regarded them all, both diffuse and nodular, as part of the same pathological condition. Trauma, toxic and infectious irritation may determine the localization, but these lesions are all manifestations of a primary disturbance in lipid metabolism.

We are dealing with a pathological change, particularly involving the reticulo-endothelial system and resulting

from abnormal or excess lipoids circulating in the body fluids, as is shown by vital staining and experimentation in the cholesterol feeding of animals. First of all, there is observed an increase of lipoids in the blood, then an infiltration of the tissues takes place. According to this hypothesis, the reticulo-endothelial system plays only a passive rôle. Infiltration occurs because the lipoids in the body fluids exceed a certain level.

There is nothing unusual about the topography of this disuse, all parts of the reticulo-endothelial system participate. Infiltration occurs in the reticular cells of certain organs and endothelial cells of blood and lymph vessels, generally, and finally, extends over into the parenchymal cells of certain organs.

In rapid development the infiltration is diffuse. In slow development the change is more localized, assuming at times a tumor-like appearance. In the course of time, there is fibrosis, occasionally necrosis and cyst formation which mask the original picture.

In the same manner the chemical content of the cells varies. In Christian's syndrome, microchemical and chemical analysis shows these cells to contain cholesterol esters, phosphatid lipid and neutral fats in varying proportions and amounts.

There has been a great deal of discussion as to why lipoids accumulate in the body fluids. Abnormal congenital predisposition has usually been ascribed to the infantile type of this disease, but this is not sufficient explanation. That disturbance of excretion may play a part seems probable. Herzenberg thought liver dysfunction

important in her case. It would seem that, superimposed upon a constitutional anomaly of lipid metabolism, a disturbance of liver function and also of the lungs, which Aschoff regards as excretory organs for fats and lipoids, causes an excessive accumulation of lipoids in the body fluids accounting for the massive storage of lipoids observed in Christian's syndrome.

A certain number of lipoids are normal body constituents. They appear in the body physiologically and become more apparent in the retrogressive changes of old age. Kawamura says that they easily pass the normal point and become pathogenic.

This view, based on animal experimentation, has not been entirely accepted, because the experiments were done on herbivorous animals unaccustomed to fats and lipoids, but recently, Kawamura and Yuasa have confirmed the observations in omnivorae, and for that reason Yuasa believes that there is no longer any reason for not applying the experimental evidence to man.

*The Conditions that Should be Regarded as Primary Lipoid Cell Hyperplasias of the Reticulo-endothelium*  
Ludwig Pick, to whom we are indebted for the foundation work in this study, separates, in his writings, the different lipid cell hyperplasias of the reticulo-endothelial system, although in describing the form of the disease which occurs most frequently in infancy, he says that protracted type of this metabolic affection seems probable. In my paper in the "Archives of Internal Medicine," I expressed the opinion that Christian's syndrome represented a form of this disease which

permitted bringing the different lipid cell hyperplasias all into closer unity. At the same time, Herzenberg's report appeared describing a case of Christian's syndrome under the title "Die Skelettform der Niemann-Pickschen Krankheit," partly confirming this opinion and presenting for the first time evidence of the familial character of this syndrome, and there seems to be sufficient ground in the literature on xanthoma to consider most of the lipid cell hyperplasias as a single disease, resulting from a primary constitutional, sometimes, familial deviation of lipid metabolism.

The clinical conditions which can be brought together as lipid cell hyperplasias, the result of a primary disturbance and of lipid metabolism are Niemann's disease, the rapidly developing syndrome of splenohepatomegaly occurring in infancy, Christian's syndrome, the characteristic skeletal form most often observed in early childhood, and Xanthoma in all the various forms described, for the most part, in the dermatological literature. These last will require further study from this point of view, to be properly brought into the grouping. Some of them will be found to be mild forms in the two preceding groups, and others will represent the adult types of this disease. There are transition cases from Niemann-Pick's syndrome to Christian's syndrome and on to the adult forms of xanthomatosis reported in the literature (Fahr and Stamm, Oppenheimer and Fishberg, and others mentioned in my previous paper). In regard to the cases of xanthoma associated with icterus and diseases of the liver, and certain kid-



ney affections, these symptoms are secondary to the lipid cell hyperplasia and also represent the manifestations of a primary disturbance in lipid metabolism. The cases showing glycosuria and diabetes mellitus fall into the same grouping, only modified by a disturbance of carbohydrate metabolism, but it may be that the disturbance in carbohydrate metabolism in such cases, results from the lipid cell hyperplasia, at least that the pathological change comes from a primary disturbance in lipid metabolism.

As for Gaucher's disease, according to Ludwig Pick, it also represents a constitutional familial affection resulting from a primary disturbance of lipid metabolism, but showing certain definite variations. In Gaucher's disease a complex lipid, principally a sphingogalactocide-kerasin, is stored in the reticulum cells of the lymph-hemopoietic system, but limited to the spleen, liver, lymph nodes and bone marrow. In Niemann-Pick's syndrome the lipid, especially a phosphatid, is stored in all parts of the lymph-hemopoietic system and no organ or tissues are immune to the deposits. As a result, the organs in Gaucher's contain large cells filled with a fibrillar protoplasm, resisting staining, quite different from the large vacuolated foamy cells in Niemann-Pick's syndrome.

In Christian's syndrome, the foamy cells contain phosphatids, but more cholesterol, anisotropic bodies and neutral fats, while in adult manifestations, usually cholesterol esters and anisotropic bodies, and sometimes, neutral fats predominate. The cells are like the cells found in Niemann-Pick's

syndrome. Oppenheimer and Fishberg observed that "There are no essential differences, in cell morphology, between Niemann-Pick's disease and the other simple forms of lipid cell hyperplasia," except, those that can be explained on the ground of the patient's general metabolic state, and as I suggested, in my previous paper, further investigation may determine that this is the only difference between Gaucher's and Niemann-Pick's disease.

In all these forms—the clinical manifestations, the anatomic and microscopic changes, and the chemical content of the lesions show great variations, but they represent the same irritative proliferation of connective elements, (i.e., reticulo-endothelial hyperplasia resulting from the infiltration of lipoids), their only difference being the nature of the lipoids concerned. The manifestations vary in clinical form according to the age of the patient, the rate of development, the intensity and the duration of the process.

Alpert, who suggests bringing all these different forms under the general head of Gaucher's disease, as familial affections due to one cause, but showing many different pictures, says "We must not be surprised that the histochemical and clinical types of Gaucher's disease multiply themselves. It is well to recognize and study these different types, but also it is well not to be troubled by their multiplication. It is natural because we are dealing essentially, with a familial disease of which, in spite of the different types, it is necessary to conserve the general unity."

It appears to me that from our pres-

ent knowledge of all these varied affections, we can place them in two clinical groups

1 Gaucher's disease—with infantile, early childhood and adult forms well correlated

2 Simple lipoid cell hyperplasias in which there is at present no unity—represented by Niemann's syndrome in infancy, Christian's syndrome occurring in early childhood, and the various types of xanthomatosis which appear in later life—representing the adult forms of this disease

These affections are identical within their own groups, and all show many analogies, but also certain specific differences in cell morphology and the chemical content of the cell. They all represent the manifestations of a primary disturbance in lipoid metabolism, and on clinical grounds with the above reservations, should be grouped together

It would seem appropriate to bring all the simple lipoid cell hyperplasias included in the second group under the general heading of Niemann-Pick's Disease. According to this interpretation, Niemann-Pick's disease would manifest itself, in infancy, particularly by spleno-hepatomegaly, extreme ca-

chexia and nervous symptoms, and would be rapidly fatal, in childhood by skeletal defects, sometimes, spleno-hepatomegaly, exophthalmos, diabetes insipidus, dwarfism, dystrophia, adiposogenitalis, anemia, and would be a progressive disease which is frequently fatal in from two to four years, in adult life the symptoms would be more diversified and the course slower, and this disease would manifest itself either by splenohepatomegaly and diabetes mellitus, icterus and certain liver disorders, or kidney affections

In conclusion, I believe I have described a remarkable pathological change—lipoid cell hyperplasia, a lipoid storage disease of the reticulo-endothelial system—"lipoid gout". This change has been studied by pathologists for a long time, but its clinical importance is not generally recognized

In my first paper, I discussed, particularly, the pathogenesis of this affection in its relation to xanthomatosis and mentioned the many conditions that are explained by such a pathologic change. I need not repeat them here, but this pathological change which affects all parts of the body should be of interest to the clinician and surgeon alike, as it suggests the manner of treatment

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# The Ketogenic Diet in the Treatment of Epilepsy

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**E**PILEPSY is a symptom-complex consisting of sudden periodic loss of consciousness, convulsive movements or both. Of the same nature are certain other phenomena referred to as epileptic equivalents, such as migraine, certain cases of periodic vertigo, periodic voracity, dipsomania and other periodic mental disorders. Epilepsy is thus a periodic reaction of the nervous system, in which various motor, sensory, visceral and psychic syndromes may occur. Levy and Patrick (1) have recently described a number of so-called pre-epileptic phenomena, which may antedate the major seizure for many years; these consist of minor, but sudden and periodic symptoms, such as pallor of the face, sense of thirst or of asphyxia, trembling, staggering, screaming, hot flushes and other disorders of momentary duration. Recognition of these early phenomena is important, as it is in the earliest stages that treatment is most beneficial. The public should be taught the significance of such symptoms. It has been estimated that there are about 500,000 epileptics in the United States. The situation demands the attention of the medical profession,

in order that progress be made in our knowledge of this condition, and that patients be treated as early as possible.

By definition, epilepsy is not a disease, but a symptom-complex or syndrome. To emphasize this, it has been proposed to discard the term epilepsy, and to speak of these conditions as paroxysmal disorders. There is no need to discard the term epilepsy if it be properly understood. It is not per se a malignant condition, neither hopeless of cure, nor ending in dementia. When dementia does occur, it is not dependent upon the severity or frequency of seizures, but is due to the cause behind the attacks. Mental deficiency is present in only about 4 % of cases. Epilepsy should be looked upon as any other symptom, such as headache. The one difference from other symptoms is the fact that each seizure constitutes a severe injury to the brain, producing changes which may in turn incite attacks. This may explain the marked tendency for seizures to recur, what is termed the epileptic habit. This vicious circle must be interrupted by treatment as early as possible.

Epilepsy is associated with many conditions. It may be said that either an organic lesion or a functional disturbance in the brain must be present

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in all cases. A vascular spasm is apparently the immediate precursor of the attack. No other fundamental factor common to all cases has been found. Some of the conditions known to be associated with convulsions are the following:

- 1 Organic disease of the brain, any disease of the brain may be accompanied by repeated convulsions. These may be listed as congenital brain disease, heredo-degenerations, brain trauma, tumor, parasitic cysts, syphilis, tuberculosis, meningitis, abscess, cerebral edema, epidemic encephalitis, encephalitis and cerebral palsy of childhood, progressive subcortical degeneration, multiple sclerosis, presenile gliosis and senile cortical atrophy.

- 2 Circulatory disorders, these include vascular anomalies of the brain, cerebral aneurism, cerebral arteriosclerosis and endarteritis, angioma, vascular spasms (Raynaud's), heart block, paroxysmal tachycardia and blood dyscrasias. Convulsions may also occur in cerebral embolism, thrombosis and hemorrhage.

- 3 Intoxications. These may be exogenous, as chronic alcoholism, lead poisoning, cocaine, absinthe or after injection of insulin. Protein sensitization may be a factor in some cases. Endogenous intoxications also cause convulsions as in eclampsia, uremia, endocrine disorders, intestinal toxemia, and disturbance of acid-base relationship (hyperventilation).

- 4 Psychic conflicts

- 5 Reflex disorders. Although reflex disorders occupied a prominent place in the etiology of epilepsy by the

older writers, it is doubtful if such is ever a true cause of epilepsy. A case reported by Block (2) suggests that reflex epilepsy occurs only in association with organic disease of the brain.

Lennox and Cobb (3) have made a critical analysis of the etiologic factors of epilepsy. They believe that there are possibly three factors involved in every case. A Pathological changes in the nervous system. It is doubtful if the brain of any epileptic is normal, although there has been little opportunity to study the brain in early cases. If normal at the start, secondary changes probably develop, increasing with time, unless the seizures be controlled. The rarity of epilepsy in cases of known disease of the brain however, suggests an additional factor. B Functional instability of the nerve cells. This may be based on a hereditary tendency (about which little is known), psychic conflicts, or more probably on complex physico-chemical changes within the cells. Among the latter, one must consider such changes as anoxemia, ionic and colloidal disturbances, change in hydrogen-ion concentration, edema and changes in cellular permeability. C Extracerebral disorders, which influence the function of the brain. Among these, are disturbances of intracranial circulation, of the autonomic nervous system, metabolism, the endocrines, respiration and the gastrointestinal tract.

The importance of the above three factors would vary in individual cases, and at different times in any given case. The analysis of the etiologic factors in a particular case is often

difficult. The initial precipitating factors may have ceased to be important, or the attacks may be a manifestation of an otherwise asymptomatic brain disease. Epilepsy may be the sole evidence of a brain tumor or of multiple sclerosis for years before other signs appear. According to Cobb, the immediate cause of a seizure may be conceived of as a vascular spasm of the brain, leading to deficient oxygenation of the nerve cells, intracellular alkalosis, electrolytic changes and edema, these being associated with increased irritability to the point of sudden discharges of nervous impulses. The apnea and muscular contractions of the attack lead to an accumulation of carbon-dioxide and lactic acid in the tissues, which reverse the metabolic disorder, and the attack then ceases.

The first principle in the treatment of epilepsy is a thorough search for the etiologic factors. The history must be carefully investigated with respect to familial nervous disorders, birth and development of the patient, nutritional disorders of childhood, food idiosyncracies, previous infectious diseases and head injuries. A thorough neurological examination should be made and repeated at intervals. This should include a roentgen-ray of the head and spinal fluid examination with measurement of the cerebro-spinal fluid pressure. In certain cases, a ventriculogram, or encephalogram (made by injection of air through a lumbar puncture) is indicated. Physical examination must be complete with special attention to anomalies, endocrine disorders, foci of infection, and the circulatory system. Laboratory examination should

include in addition to the spinal fluid examination, study of the blood, urine and stools. In certain cases, basal metabolism, protein sensitization tests and a roentgen-ray examination of the gastro-intestinal tract may be of value. The Wassermann test should never be neglected. Other examinations may be indicated in certain cases. Some investigation of the psychic life of the patient should be made in all cases. Frequently however, all these examinations will reveal little that seems significant.

The second principle of treatment is that the attacks must be stopped as soon as possible, as they tend to recur. Cure of epilepsy is possible only by prevention of attacks for a long period of time. To correct the suspected etiological factors, without giving symptomatic treatment may result in failure. Regardless of the etiology, all cases should receive symptomatic treatment. This is true even in cases of brain tumor, where such treatment may not be necessary for very long, but should be given for a time after operation. The practice of allowing patients to have repeated seizures for a long time without treatment, because of hesitation in diagnosis cannot be too strongly condemned. Convulsions tend to recur, and convulsions from any cause may become epilepsy.

In each case, attention must be paid to all possible etiologic factors. Surgical treatment may be indicated as in cases of brain tumor, abscess, arachnoid cysts or depressed bone. Non-specific protein treatment or desensitization may be indicated in a few cases. Endocrine disorders may indicate glandular therapy. The patient

should always be placed in the best possible physical condition. In regard to general hygiene, avoidance of alcohol, sexual excess, physical and mental exhaustion and attention to correct eating habits and intestinal elimination are recommended in all cases. Muskens (4) places first emphasis on hygienic methods, while Collier (5) states that he has seen no particular value in them. Psychotherapy is a valuable adjunct in all cases. Among the drugs, bromides have always occupied first place. Although much abused, today we are able to administer bromides scientifically, due to the work of Ulrich (6) and others. The action of bromides is dependent upon the relation to chlorides in the body, in order to obtain therapeutic action as well as to avoid bromide intoxication, this bromide-chloride ratio must be kept within certain limits. There must be a proportionate intake of both salts. Wuth (7) has devised a method for estimation of the bromide content of the blood which is of aid in regulation of the dosage. Because of ease of administration, luminal has largely displaced bromides, unfortunately, it is often inadequate for minor seizures. Potassium boricartrate is another drug of value, but less effective (8). Other drugs may be indicated in specific cases.

Diet has always received attention in the treatment of epilepsy. Various diets have been advocated on an empirical basis. Low protein diets have been used although biochemical investigations have shown no disorder of protein metabolism. Saltfree diets have been of value in association with the use of bromides. Low carbohy-

drate diets have been used in accordance with the hypothesis of Cuneo (9) that there is a faulty intestinal digestion of carbohydrates. Many other diets have been proposed.

The ketogenic diet has been developed on a more rational basis. No one denies its beneficial effect in certain cases. Although some state that its effect is due to elimination of foods to which the patient is sensitized, or to regularity in eating, these views cannot be upheld. The diet was developed on the basis of the effect of starvation. Fasting was used years ago in epilepsy as in other diseases. Conklin (10) an osteopathic practitioner was the first to use it extensively and reported remarkable results. In 1921, Geyelin (11) reported on 26 cases, starved for 20 days, attacks ceased in 16 cases, and in 2 did not return within a year. Lennox and Cobb (12) have recently reported on 27 cases, starved for 4-21 days, attacks ceased in 10, and 10 others were improved. Fasting has but temporary results, the attacks usually recurring at the end of the fast.

As fasting cannot be prolonged, and as similar bio-chemical changes may be produced by a ketogenic diet, Wilder (13) in 1921 proposed treating epilepsy with a ketogenic diet, a low carbohydrate-high fat diet such that a ketosis is produced and maintained. The ketosis is shown by the marked increase in ketone bodies in the blood urine and alveolar air. There is also produced a marked rise in uric acid in the blood, slight fall in pH of the blood, slight fall in carbon-dioxide combining power of the blood and a change in carbohydrate metabolism, the fasting blood sugar is low and the



glucose tolerance curve shows a delayed rise, higher than normal, with a delayed fall. Non-protein nitrogen, calcium, phosphorus and chlorides show no change (14).

There are many reports in the literature tending to show that at least a group of epileptics show a wide variation from hour to hour and day to day in the hydrogen-ion concentration of the blood and urine, although within normal limits, preceding attacks, there is a tendency toward an alkalosis, and following attacks there is a temporary acidosis. It has been shown that a sudden shift from an acidosis to an alkalosis by the administration of alkali may increase the frequency of seizures (3), the same result occurs with hyperventilation. This may be compared with the muscular cramps of tetany, produced by over-dosage of alkali. It has also been found that carbon-dioxide, as in rebreathing, stops epileptic attacks as well as persistent hiccup and other muscular spasms. In addition to the change in hydrogen-ion concentration, anoxemia and electrolytic changes are probably important. Acidosis produced by the administration of acid-forming salts is only of temporary benefit, Lennox and Cobb believe this is due to electrolytic changes which counter-act the acidosis, while Peterman (15) believes this shows that acidosis is not the essential factor. Peterman believes that the diet is beneficial because of a sedative action of the ketone bodies on the nerve cells, Lennox and Cobb believe that the diet induces complex physico-chemical changes within the nerve cells, among which a change in the hydrogen-ion concentration is an important

item. Further work is needed to fully explain the action of the diet. What effect the change in carbohydrate metabolism, or the increase in uric acid in the blood may have is uncertain.

The use of this diet has been more successful in children than in adults because it is easier to produce and maintain a ketosis in children than it is in adults. No harmful results have occurred and children have been maintained on the diet through such diseases as whooping cough, scarlet fever and measles. What might develop from the use of this diet over a period of years is not known. Fortunately in many cases, the diet need not be used over a very long period of time. It is sometimes possible after freedom from attacks for some months, to gradually revert to a normal diet without recurrence of attacks. There are cases reported in which attacks have not occurred for as long as 3-4 years after resumption of a normal diet.

The results obtained by the ketogenic diet vary. Little improvement is to be expected in cases of long duration, or marked mental deterioration or of gross organic disease of the brain. In certain cases, the attacks cease and do not return after gradual resumption of a normal diet. In others, the attacks reappear on any change in diet. In some cases, the diet has to be supplemented with a sedative drug. Likewise certain cases treated with drugs will do better with the addition of the ketogenic diet. Some cases receive no benefit from the diet. Some benefit may be obtained in certain cases with brain pathology, as in encephalitis or cerebral palsy of childhood. That adults may also receive benefit is shown

by the report of Barboika (16), he stated that of 32 cases, attacks ceased in 7 and diminished in frequency in 12. It is impossible to predict whether a patient will be benefited or not. The most favorable cases are those of short duration in children without evidence of brain disease or of mental deficiency. Talbott (17) reported marked benefit in 30% of such selected cases. Helmholtz (18) after five years experience reported cessation of attacks in 31% and marked benefit in 23%, or good results in 54% of cases. The diet seems particularly beneficial in cases of frequent petit mal, in which luminal is often ineffective. Peterman has reported that 20 of his cases are now on a normal diet and have been free of attacks from 6 months to 3 years. The improvement obtained seems definitely proportional to the degree of ketosis developed. In view of such results, the ketogenic diet must be accepted as a valuable addition to the treatment of certain cases of epilepsy.

The diet must contain the caloric requirements of the individual according to their age, weight and height. It must also contain the protein requirement, which may be accepted as  $\frac{2}{3}$  grams per kilogram body weight for adults, and 1 gram per kilogram body weight for children. The carbohydrate and fat are then adjusted according to well known principles as to produce a ketosis. The ketogenic ratio (relation of fatty acids to dextrose produced) must exceed 2, and frequently a ratio of 3 or 4 may be necessary. Vitamines are to be supplied, as in fats, green vegetables, cream and eggs. Palatability must be given attention. There is no limita-

tion of salts. In some cases the diet must be supplemented with inert material to avoid hunger. As the diet tends to induce constipation, attention must be given to this matter. The patients must be intelligent and cooperative. Both children and adults take the diet readily when willing to cooperate. It is often difficult to get cooperation, as patients state that have tried various diets without benefit, or that they do not have indigestion. It is thus necessary to explain the purpose of the diet at the start. Urinalysis must be done at frequent intervals in order to regulate the diet so as to obtain a ketosis of sufficient degree. Patients may be taught how to test the urine, and sometimes this is of aid in maintaining their interest. Simple methods of calculating the diet have been devised by McQuarrie and Keith (19) for children and by Barboika (16) for adults. It is usually best to begin with a 2-3 day fast, but this is not always necessary. It has been my practice to give small doses of luminal until a ketosis is developed, and then to withdraw it if possible.

It is not my intention at this time to report any further statistics. Some examples of the response to the diet are briefly reported.

*Case 1.* A colored girl, aged 16 yrs was first seen in April 1927. Generalized attacks had been occurring from one to three times a month for two years. She stated that she had taken drugs with little benefit. The usual clinical investigations did not reveal the cause of the attacks. She was placed on a ketogenic diet, and had no further attacks from the start of the diet. One year later, no attacks having occurred within this time, she voluntarily abruptly broke the diet. She continued free of at-

tacks for five months longer, when she again had a seizure. She was again placed on the diet, and has been free of attacks. No other medication was given during the treatment.

This case represents a very favorable effect of the diet. It is possible if the change to a normal diet had been more gradual, the attack would not have occurred five months later. While it may not be possible to bring her back to a normal diet, evidently the diet will control her attacks whenever necessary. That the diet is superior in this case to proper drug treatment cannot be said, but that it is effective cannot be denied.

*Case 2* A white male, aged 18 yrs, was first seen in September 1927. He had been having 3-4 major convulsions a year and frequent petit mal attacks since the age of 4 years. The usual investigations revealed little, there was a family history of migraine. He was placed on a ketogenic diet, and remained free of attacks for five months, when he broke his diet, and had another seizure. He would not cooperate with further dietary treatment.

In this case also, the diet seemed to have a definite beneficial effect, although it may not have been possible to revert to a normal diet without return of seizures.

*Case 3* A child of 6 yrs was first seen in May 1927. She gave a history of high fever and convulsions, followed by a left hemiplegia at the age of 15 months. Convulsions had continued from that time, Jacksonian in type, and occurring once a week to several times daily. A diagnosis of encephalitis or cerebral palsy of childhood was made. She was placed on a ketogenic diet and small doses of luminal, which she was taking when seen. With the addition of dietary treatment, there has been a marked diminution in frequency of attacks. The interval between attacks is now frequently as long as six weeks. In addition there has been an increased mental alertness, with decreased irritability.

This case represents a type in which it is believed that the addition of the ketogenic diet to drug treatment gives better results

than either alone. By such combined treatment, one may be able to avoid the high dosage of drugs sometimes necessary.

*Case 4* A child of 3 years was first seen in February 1928. The child presented a marked precocious development or pubertas praecox. No definite basis was found for the precocious puberty after thorough study, including a craniotomy with exposure of the pineal region. The neurological and other examinations gave no abnormal findings except the precocious development. This child had frequent petit mal attacks, in spite of the administration of luminal, at least 3-4 times daily. After beginning the diet he went a week without any attacks being observed. This improvement has continued under combined treatment. Withdrawal of the luminal ( $\frac{1}{4}$  grain twice daily) or a break in the diet results in increased frequency of seizures. Under combined treatment, attacks never occur more than once daily, and at intervals of 3-6 days.

In this case, it is also felt that combined treatment gives better results than either alone.

*Case 5* A young man aged 22 yrs was first seen in January 1928. He had had generalized convulsions from the ages of one to seven years, and petit mal attacks beginning at the age of 16 years. These attacks occurred about 10-12 times monthly. He had been treated with luminal without benefit. He was placed on a ketogenic diet, and in spite of a marked ketosis being maintained for 8 weeks, showed no improvement. The early onset, and history of long dry labor, suggested that a birth injury was probably the cause of the attacks in this case.

This case represents a type in which no improvement was obtained by the ketogenic diet after two months. It is possible that the long duration of the attacks and probable organic changes in the brain were responsible for the lack of improvement.

#### SUMMARY

Epilepsy is a syndrome which may be associated with many conditions

## The Treatment of Epilepsy

Rational treatment should include first a thorough search for etiologic factors in each particular case. Regardless of etiology however, an effort must be made to stop the attacks so that the vicious circle known as the epileptic habit does not develop. Such symptomatic treatment should be given as early as possible. Luminal and bromides are the two drugs of choice in symptomatic treatment. The ketogenic diet represents an addition to these methods, which has a more rational basis than other diets proposed. It is not to be considered as a cure-all, but the evidence indicates that it must be accepted as a valuable aid in certain cases. Its exact place in the treatment of epilepsy, as well as a full explanation of its action remain to be determined.

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# Diffuse Scleroderma, With Case Report and Autopsy Findings\*

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**S**CLERODERMA is a rare disease in the experience of any one observer. This is especially true of the diffuse form of the disease. Osler (1) did not see his first case until 1891, during the fourteen year period from 1891 to 1905 he saw a total of only twenty cases of scleroderma of all types (2). While the disease is said to be relatively more frequent in the United States than in other countries, Lewin and Heller (3) were able to list but thirty-two cases as having been reported from the North American continent, out of a total of 451 cases available for study of geographical distribution. Allbutt (4) gives the American incidence as 2 in 16,863. Hebra (5) never saw a single case. Out of a total of 7000 patients at his Berlin Clinic for nervous and mental diseases, Oppenheim (6) had only 7 cases of scleroderma. Since Watson (7) first described Curcio's case in 1754, there is mention of only some seven hundred cases in the literature.

Scleroderma has been recognized as a definite disease entity ever since Thirlial's (8) paper (1854). Observation during the past century and a

half has convinced numerous observers that scleroderma is indeed an entity, despite the various distinct clinical types (Sequeira (9), Stelwagon (10), MacLeod (11), Schamberg (12), Castle (13), Osler (2), Robinson (14), Lewin and Heller (3), et al). Crocker (15) classifies the disease into three groups (1) Diffuse symmetrical scleroderma (2) diffuse circumscribed, usually unsymmetrical scleroderma (morphoea), and (3) diffuse unsymmetrical scleroderma. He inclined to the opinion that the sclerema of infancy might be a separate, albeit related condition. Stelwagon (10) simply classifies it into the diffuse and circumscribed forms.

While there is much clinical evidence to agree with the above authorities, a study of the literature reveals that there has been unnecessary confusion regarding nomenclature. Analysis of some of the cases reported as conforming to the criteria of Herxheimer and Haitman (16) for the diagnosis of acrodermatitis chronica atrophicans, raises a serious question as to the correctness of such an interpretation (Kingsbury (17), Kanaky and Sutton (18), and Robinson (14)). Many of the cases have been characterized by signs common to both conditions. For this reason and because

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or paucity of descriptive exactitude in some others, any attempt to tabulate the relative frequency of the diffuse and localized forms of the disease is doomed to failure. And if we accept the inherent unity of the various clinical forms of the disease, such a labor would not be fruitful or a great deal of light on the pathogenesis of this curious disease.

The literature contains much of fancy and little of fact to help us towards a better understanding of the etiology of scleroderma. Lewin and Heller (3) viewed the disease as an angioneurosis, a trophoneurosis or an angio-trophoneurosis. The origin of the disease in some obscure nervous or trophic lesion has since received wide endorsement (Cockayne (19), Crocker (15), Jacquet (20), Steven (21), Josephovitch (22), Stelwagon (10), et al). Williams (23) recently presented a patient with undoubted involvement of the nervous system. His case, however, presented some unusual features. It is not strange that the nervous system should be affected in the course of a disease showing such an extensive fibrosis of the internal organs as does scleroderma. For the most part the authors who favor involvement of the central nervous system as explanatory of the clinical manifestations of the disease, are able to cite little more than circumstantial evidence in support of their views. To credit a disease with such definite local pathological and clinical manifestations as due to a trophic disturbance fails to offer a concrete basis for the fuller understanding of the disease.

The thyroid gland has been implicated by numerous observers (Hek-

toen (24), Uhlenhuth (25), Sandmuller (26), Graham Little (27)). Graham Little's report is of especial interest. His patient was operated upon by Kocher for the purpose of a homoplastic thyroid graft into the thorax in 1911 and again eight months later in 1912. There was definite improvement of the sclerodermatous condition on both occasions. But in 1913 when again consulted Kocher advised against a third implantation and contented himself with administration of the gland extract. The graft, therefore, failed of effecting a cure—the possibility of absorption of the graft has to be kept in mind, of course. This patient, moreover, showed an equally marked retrogression of the skin manifestations subsequent to the removal of some carious teeth. It is further worthy of note that Graham Little's patient had at various times exhibited signs and symptoms of overactivity as well as of underactivity of the thyroid gland.

Hektoen (24) presented details of a case of scleroderma coming to autopsy with a significant reduction in the iodine content of the thyroid gland, as determined by chemical analysis. His patient also showed an hyperplasia of the chromophilic cells of the pituitary gland—possibly a compensatory phenomenon. It is by no means unlikely, however, that the thyroid alteration in his patient was incidental to rather than causative of the scleroderma.

Sequeira (28) described four cases associated with Graves' disease. He concluded, however, that "It is true that a certain proportion of the cases are associated with affections of this

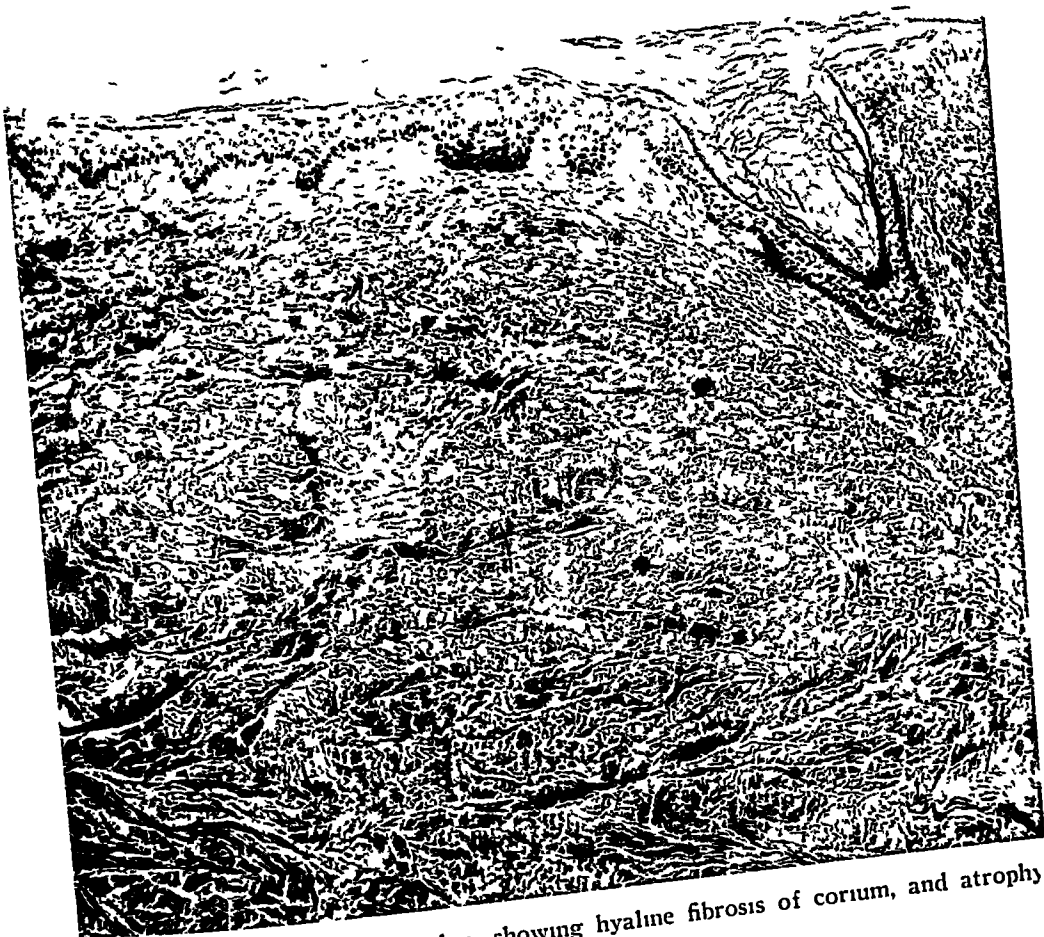


FIG 1 Low power view of skin, showing hyaline fibrosis of corium, and atrophy of skin structures

gland (thyroid) but there is nothing to warrant the conclusion that alterations in the activity of the gland or of its secretion are actually causative of scleroderma

Osler (1) was unable to convince himself of any specific action of thyroid extract feeding on the sclerodermatous state, nor was he able to report definite improvement in his patients as the result of such medication

Castle (13) has carefully reviewed the literature on this subject. He favors the view that the disease is of combined endocrine and nervous origin but refuses to implicate any one gland. He favors the concept that

failure of any one of the endocrine organs may so disorganize the harmonious interplay of the glandular secretions as to evoke this rare syndrome

The case presently to be reported may, on superficial analysis, be cited as further evidence in favor of the thyroidal origin of the disease. But a more careful scrutiny of the facts reveals that the changes noted in the thyroid were not in any way specific but merely such as accompanied the stroma increase of the other organs

The very frequency of thyroid disease and the relative and absolute rarity of scleroderma are almost prima



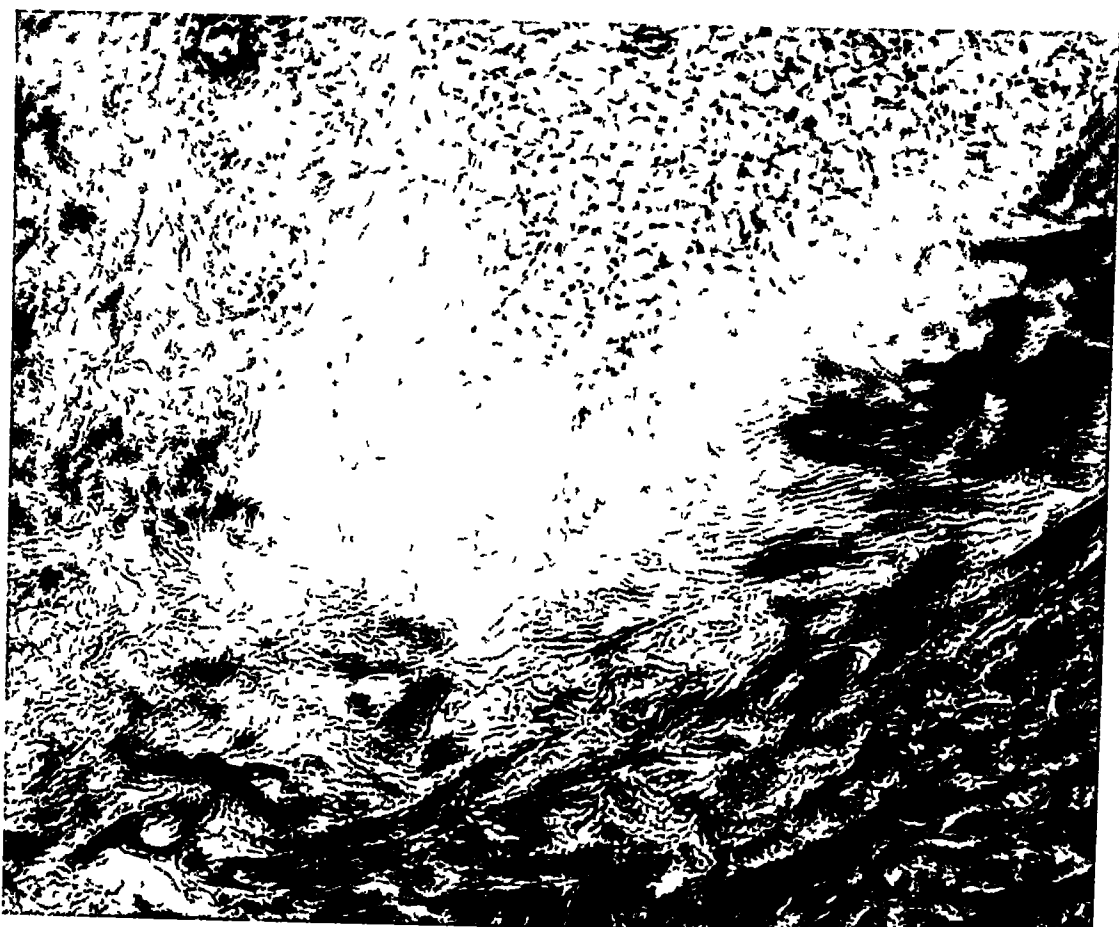


FIG 2 Hyaline fibrosis of subcutaneous tissue Atrophy of adipose tissue

facie evidence against acceptance of the thyroid etiology

That a disease as frequently accompanied by pigmentary changes as is scleroderma should be coupled with possible supra-renal disease is not surprising

Lewin and Heller (3) collected 144 cases in their series of 508, showing an increase in pigment Schultz (29) reported the case of a girl with scleroderma of the arms and legs, accompanied by pigmentation of the face and neck and by muscular atrophy The disease ran a rapid course and terminated fatally four months after onset At autopsy the left supra-renal gland was found to be increased in size, adherent to adjacent structures

and to present a few small grey nodules He failed to present a detailed histological description of sections of the gland, thereby materially detracting from the value of his observations

Winfield (30) described a case simulating Addison's and Raynaud's disease, with marked benefit from administration of supra-renal extract A second case coming under the care of the same author showed equally marked improvement under similar therapy This aspect of the subject is well covered by Castle (13)

In our case the adrenals also showed some changes Yet the clinical manifestations were not indicative of severe adrenal disease It is not unlikely that adrenal changes may be responsible

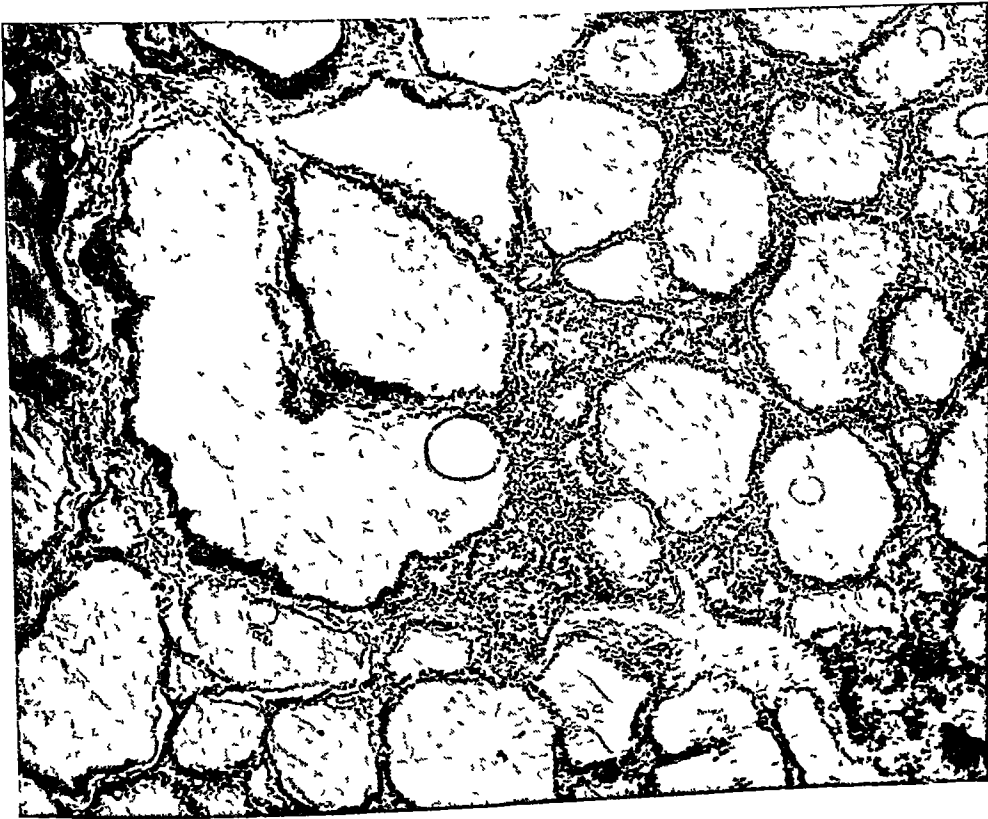


FIG 3 Thyroid Abundant colloid and slight fibrosis

for the pigmentary changes and that seems a more logical, if conservative, view than implication of these organs as the basis for all the sclerodermatous changes

Among other etiological considerations, the possibility of a syphilitic basis for this disease has been propounded (Schamberg (12), Jackson (31), Whitehouse (32), et al) Here the same objection as was raised in regard to thyroid disease holds good. Not unlikely, scleroderma has at times been manifested in demonstrably luetic patients. But we must be cautious in evaluating the significance of such a relationship. Syphilis is on the increase, scleroderma is not, scleroderma is at most only a very rare accompaniment of syphilis.

Ayres (33) has recently raised a question as to the possibility of arsenic poisoning being responsible for scleroderma. He cites cases in which he was able to demonstrate arsenic in the urine. But he admits that such a finding is not unusual in apparently healthy controls. In view, also, of the increased incidence of arsenical medication it would not be illogical to expect an increased incidence of scleroderma. Ayres urges histochemical investigation of the tissues but this is not a practicable plan (Weller (34)). Bramwell (35) reported nine cases, all males, in whom the scleroderma started in the hands, apparently from the use of cold chisels. Sequeira (36) reported the case of a youth who bruised himself severely across the

lower left chest and six months later noticed increased pigmentation over the area. At a later date he developed an extensive morphea over this area. Roberts (37) also reported a case in which trauma was considered the immediate cause of morphea. Fox (38) showed a case of morphea guttata before the Dermatological Section of the Royal Society of Medicine in a woman who had been sunburnt. The lesion appeared over the sites of the blisters raised by the sunburn. Bancroft (39) reported the case of a girl who developed scleroderma and in whose blood he was able to demonstrate the presence of filariae.

Wolf and Vallette (40) have recently attempted to show that scleroderma is related to a disorder of the calcium and phosphorus metabolism. They present the detailed report of a patient with localized deposits of calcium at the edges of the sclerodermatous areas. They quote extensively from the literature on related conditions. Although their patient did not show a significant alteration of the serum calcium values, they claim that such a deviation need not necessarily occur to prove their contention.

In this connection Longcope's (41) observations are of interest. He noted hypoglycemic crises in a sclerodermatous subject when breakfast was omitted for the purpose of a study of the basal metabolism. Careful study of the blood chemistry of this patient failed to reveal significant changes other than persistently low blood sugar values as compared to the accepted average readings of normal controls. Nevertheless, it is worthy of note that there is a very definite relationship

between the blood sugar content on the one hand and the blood phosphorus value on the other. And in some at present unexplained manner there is a reciprocal relationship between the blood phosphorus and the serum calcium content. As Longcope points out, however "the disease affects the connective tissues of the entire body and the stroma of all organs may become involved in the pathologic process." He, therefore, advises caution in interpreting the findings in his series as necessarily indicative of an endocrine imbalance, since "the symptoms may have to be looked upon as secondary phenomena and not as indicative of any disturbances in the glands of internal secretion that could produce the disease." This aspect of the subject is worthy of further study.

Warthin (42) has recently drawn attention to the possible rôle of the reticulo-endothelial system in the causation of acrodynia (Swift's disease) and pellagra. In this connection Rowland's (43) concept of the possible implication of the reticulo-endothelial system as an etiological factor in the evolution of xanthoma should also be kept in mind. While it may at present seem far fetched to link up scleroderma, acrodynia, pellagra, xanthoma and other obscure skin manifestations, such a possibility cannot be dismissed lightly. Warthin (44), indeed, suggests that scleroderma may be a variant of the gouty state of altered metabolism, just as uric acid gout is characterized by a disturbance of uric acid metabolism, so may certain other states be the reflection of a disturbance of the lipid metabolism abetted by a disability on the part of the re-

endothelial system in its storage mechanism (lipoid gout), while others are characterized by a hyaline sclerosis (sclerotic gout). Wolf and Little (40) make out an analogous condition except that they stress the altered calcium and phosphorus values of the organism. It is pertinent to note, however, that many of the reported cases showed a prompt and marked amelioration of their symptoms as the result of an altered dietetic regime. This possibility is at least worthy of further

#### CASE REPORT

G. F., housewife, age 31, an Armenian born in Greece and living in Michigan many years, was admitted to the University Hospital Department of Internal Medicine, August 1, 1928, because of swelling of the hands and feet.

*Present illness* began some four years previous to admission with pain, numbness and a feeling of warmth in both hands and both ankles, more severe on the hands.

These symptoms persisted for one year. The swelling and redness subsided but the pain continued. One month before admission she complained also of pain, swelling and stiffness in the hands. Shortly before admission the swelling of the knees and ankles returned and at the time of admission there was swelling of the knees, hands, and hands, with stiffness and pain in movement of these joints. During the course of the present illness there were gastro-intestinal symptoms consisting of anorexia, nausea, flatulence, vomiting and diarrhea. These symptoms were most marked about one month before admission. At this time she also suffered with general malaise, fever and chilliness, restlessness and insomnia. At times she had slight headache.

She lost about 10 pounds in the six months preceding admission.

*History* She had measles as a child and no other exanthem. There had been no tuberculous contacts. Before tonsillectomy in April, 1927, she had been subject

to frequent headaches but at only infrequent intervals since. Seven years before admission she was troubled at times with generalized pain in the legs, but of a mild character. At that time, also, she had vague digestive disturbances, characterized by "sour stomach and gas on the stomach." Occasionally nausea and generalized abdominal cramps were associated features. In April, 1927, her tonsils were removed. On July 29, 1927, she was admitted to the Gynecology Department, complaining of pain in the right side of the abdomen of about five years' duration, noticeable since the birth of her second child. At that time (July 1927) she also complained of ringing in the ears, especially the right. The diagnosis at that time was Old lacerations of the pelvic floor and cervix uteri, visceroptosis, salpingitis of the Eustachian tubes. Surgical treatment was not advised.

There had been no history of venereal disease. She had had three pregnancies, the first of which terminated in miscarriage at seven months. She started to menstruate at 13, every 20 days, lasting 6 days, without pain. Her last menstrual period (previous to admission) was on July 22, 1928. There had at times been a profuse leucorrhoeal discharge necessitating the use of a napkin. Her husband has been in good health.

All her family were killed abroad during the war and she was unable to give further details as to their previous health. Physical examination revealed a fairly well nourished, slight female. The skin over the hands and feet was smooth, shiny, thickened and tense. The nails were not remarkable. The degree of pigmentation of the skin was compatible with her racial origin. The joints of the wrists, hands, ankles and feet were swollen and slightly tender. Passive movement of the fingers, toes, wrists and ankles was painful. There also was pain on active movement at the shoulders and elbows. There was some limitation of motion of the lower extremities due to pain. There was no perceptible muscle atrophy. The hair showed nothing significant. Except for a very slight enlargement of the cervical glands, the lymph nodes showed

nothing remarkable. There was slight suggestion of exophthalmos, but the thyroid was not palpably enlarged or adenomatous. The fundi were negative as also were the heart and lungs. The blood pressure was 115/65. Examination of the abdomen revealed slight tenderness in the right lower quadrant on deep palpation. Examination of the nervous system was entirely negative.

*Laboratory Examination* *Urine* Several specimens were negative. One specimen, 8-15-28, showed a trace of albumin with many white blood cells and rare granular and cellular casts. On 9-24-28, a catheterized specimen contained 20 red blood cells per high power field with some clumps of red blood cells. *Blood* Hemoglobin 75 per cent on two occasions. Red blood cells about 4,000,000 on three occasions. White blood cells varied considerably. During her first three weeks in the hospital the white blood count was 8000 to 9000. During the next month it ranged from 12,000 to 24,000, the highest count being found during a complication of pneumonia. The final counts ranged around 10,000 to 12,000. The differential counts were not abnormal. The last routine blood study about twelve days before death showed hemoglobin 55 per cent, red blood count 2,840,000 and white blood count 10,500. The Kahn test on the blood was negative. *Stools* Three specimens were negative. *Sputum* Four specimens were not remarkable. Agglutination tests for B abortus, B typhosus and B paratyphosus A and B were negative. Blood culture negative. Urine culture yielded only B coli B M R 12-3-28, plus 56 per cent, 12-5-28, plus 20 per cent (tests reported as unsatisfactory). *X-Rays*—studies of right foot and right hand on August 3, 1928, showed no evidence of arthritis. Three X-ray examinations of the chest were reported as follows. 9-11-28—"Marked increase in the cardiac area. Very prominent enlargement of the left ventricle. Partial loss of the lung markings of the lower left side suggestive of a thin layer of fluid." 9-24-28—"Loss of lung markings in the lower left is more marked, suggestive of fluid or possibly consolidation. The cardiac shadow appears to have increased in size and we feel its con-

tour would be suggestive of pericarditis." 10-9-28—"Marked increase in the cardiac area. Hypertrophy of the left ventricle, also the right auricle. Slight thickening of the interlobar pleura on the right side. Some increase in the hilum shadows, possibly due to their enlargement. Lung fields clear."

*Course in Hospital* During the entire stay there was an irregular fever averaging 100° to 101° F. There was a persistent tachycardia averaging 100 to 120. Respiration rate was between 20 and 30. There was little change in symptoms for several weeks after entry except that slight cough with mucoid sputum developed. A careful search for foci of infection was made. Nothing was found other than caries of some of the teeth. One tooth was extracted on 8-8-28. About the first of September she began to complain of pain under the sternum particularly, and pain elsewhere in the chest difficult to localize. On September 10th, dullness, râles and bronchial breathing were heard over both bases. Several days later there was a suggestion of pericarditis by X-ray. The physical signs of pericarditis or effusion were absent. She was very ill at this time and recovery was doubtful. However, she gradually improved. All during this time she complained bitterly of joint pains previously mentioned and pain under the sternum. Treatment was entirely symptomatic, aimed particularly at relieving the joint symptoms. Her entire course in the hospital was steadily downward with variable periods of improvement and exacerbation. The skin gradually and steadily became firmer, less elastic and more deeply pigmented. Sweating decreased until it was almost absent. The skin was smooth, cold and shiny. These changes were most marked in the areas already mentioned, and in addition the skin over the whole body became involved to some degree. It became difficult, almost impossible, for the patient to move the extremities because of the stiffness of the skin. Finally, the face was so involved that she could open her mouth only a fraction of an inch. She grew gradually weaker and died 12-18-28.

*Necropsy* (December 19, 1928, at 11:15 P M., twenty-eight hours after death) The

body was that of a poorly developed, thin, dolichomorphic adult female, 146 centimeters in length. There was marked emaciation. The head was symmetrical and showed no sign of trauma. The features were pinched and drawn. The pupils were in the intermediate position, the right slightly larger than the left. The irides were brown. The neck was medium in length. The thorax was long, narrow and flat. The abdomen was scaphoid. There were three small decubital ulcers over the sacrum, the largest being about 1 centimeter in diameter. There was also a small decubital ulcer over each acromial process. No anomalies of development were noted. Both legs and both arms were flexed at an angle of about 35° and could not be straightened out. The inability to straighten out the limbs was due to the tightness of the skin. There were no surgical wounds, scars or signs of trauma.

The skin was dark brown in color, the pigmentation uniformly distributed throughout. The skin was smooth, dry and shining. Over the bony prominences it was drawn tight like the head of a drum. It had entirely lost its elasticity and cut like hard leather. About the knees and elbows it was drawn down so tightly as to fix those limbs in a position of partial flexion. The skin broke and cracked with ease on attempted manipulation. The subcutaneous tissues shared in the firmness of the skin and appeared like scar tissue in texture. The hair was dark and abundant. The body hair was of normal female distribution. The teeth were in poor condition. The mucous membranes appeared normal. The muscles were markedly atrophic. Rigor mortis was present. The panniculus was extremely scant. There was no edema. Body heat was absent. There was hypostasis of dependent parts. There was nothing abnormal noted about the mouth, nose, ears, external genitalia or anus.

A section of cord was removed from the lower thoracic region. This showed no gross evidence of tract degeneration or other pathology. Permission for opening the head was not obtained.

The main incision revealed a scanty panniculus and atrophic, poorly developed mus-

cles. The abdominal cavity contained 300 cubic centimeters of clear yellow fluid, no gas. The omentum hung free in the abdominal cavity. The liver edge was six centimeters below the ensiform, even with the rib margin in the right midclavicular line. The spleen was just above the rib margin. The bladder was contracted. The other abdominal organs were in normal anatomical relationship. The diaphragm was at the level of the fourth rib on the right, the fifth interspace on the left. The mammae were of the usual multiparous type. The costal cartilages cut with ease. The sternum showed no change in consistency. The left pleural cavity contained about 600 cubic centimeters of clear yellow fluid. There were a few light adhesions over the apex. The right pleural cavity contained about 400 cubic centimeters of clear yellow fluid. The lung margins were separated by about four centimeters in the anterior mediastinum. The cardiac apex was in the fifth interspace, almost in the anterior axillary line. The thymus could not be demonstrated grossly in the thymic fat. The pericardium was markedly distended and under pressure. The sac contained about 450 cubic centimeters of clear yellow fluid. The pericardium showed no thickening and there were no adhesions.

The heart measured 12 x 9 x 6 centimeters and weighed 280 grams. The heart was smaller than the cadaver's right fist and appeared reduced in size. The left ventricle, in rigor, made up the whole apex, and it was the left border of the pericardium rather than of the heart that reached to the anterior axillary line. The musculature of the left ventricle averaged 18 millimeters and showed a moderate brown atrophy. The cut surface showed many small irregular areas scattered through the musculature. These areas were orange-yellow in color and most marked under the epicardium, with strands extending inwards. They varied in size but were all quite small. No part of the musculature was free of these minute spots. The mitral orifice admitted two fingers and the flaps were slightly thickened. The aortic valve admitted the examiner's thumb, the cusps were negative. The musculature of

the right ventricle averaged about five millimeters, about two millimeters of which were fat. The musculature conformed in appearance to that of the left. The tricuspid valve admitted two fingers. The flaps appeared normal. The pulmonary valve admitted two fingers and also showed normal cusps. The coronary vessels were patent throughout and showed only slight evidence of sclerosis.

The left lung measured 21 x 18 x 7 centimeters and weighed 420 grams. There were a few adhesions at the apex. These were readily separated. The lung was air containing throughout. The surface was reddish-grey in color. Section showed some edema and congestion but no consolidation. There was no evidence of tuberculosis. The right lung measured 25 x 17 x 5 centimeters, and weighed 560 grams. There were no pleural adhesions. The upper two lobes were gray in color and of normal consistency but the lower lobe was reddish purple in color and felt firm. On section this part of the lung showed marked edema and congestion. The lobe was partly atelectatic but there were no definite areas of bronchopneumonia and pus could not be squeezed out of the bronchi. There was no gross evidence of tuberculosis. The bronchi appeared normal. There was moderate hyperplasia of the bronchial nodes. The pulmonary vessels were negative.

The aorta appeared normal in size and showed no gross signs of syphilis and only a slight degree of atherosclerosis. The thoracic portion of the esophagus was negative. The thoracic duct was not dissected. The thoracic vertebrae were negative.

The neck organs were removed at the level of the thyro-hyoid membrane. Larynx. The vocal cords were in the cadaveric position. The larynx showed neither ulceration nor neoplasm. There was a moderate degree of congestion of the tracheal mucosa which otherwise was negative. The cervical portion of the esophagus was negative.

The subcutaneous tissues about the thyroid gland showed a marked thickening and serous infiltration and appeared like edematous scar tissue. The thyroid was not en-

larged and showed approximately normal colloid substance. The parathyroids showed no gross change.

The cervical lymph nodes were not enlarged. The cervical vessels and nerves appeared normal. The deep muscles of the neck were atrophic. The cervical vertebrae were negative.

The peritoneum was smooth and shining and there was no evidence of peritonitis. The spleen measured 14 x 9½ x 5 centimeters and weighed 230 grams. It showed some congestion and a moderate degree of lymphoid hyperplasia.

The intestines, large and small, were entirely negative grossly. The appendix measured 7 centimeters in length and was normal in position. It was free of adhesions and showed no evidence of previous inflammation. The duodenum was slightly bile stained. The bile passages were patent. The ampulla was about 8 centimeters distant from the pylorus. The stomach showed multiple petechiae but no ulceration. The mucosa had a smoothed out appearance.

The pancreas was normal in size and consistency and of normal appearance on section. The liver measured 25 x 17 x 11 centimeters and weighed 1440 grams. The capsule showed several old scarred areas. Two of these were at the lower border and caused a dimpling of the surface. The largest scar was on the diaphragmatic surface of the liver and extended into the substance of the organ. On section the organ showed congestion and a diffuse increase of stroma. The gall bladder showed no gross pathology. The portal vein was negative. The mesentery showed only a very small amount of fat. The mesenteric lymph nodes were somewhat hyperplastic.

The left adrenal was closely attached to the kidney but had a distinct capsule. On section the medulla showed far advanced autolysis, the cortex a moderate lipoidosis. The right adrenal was also closely attached to the adjacent kidney but with a distinct capsule intervening between the two organs. It conformed in all appearances to the left adrenal.

The left kidney measured 11 x 6 x 4 centimeters and weighed 150 grams. The cap-

sule stripped with ease, leaving a smooth surface. The surface showed many small dark brown specks. Between these were irregular areas of lighter brown pigmentation and irregular yellowish patches, giving to the organ a remarkable color effect. On section the cortex showed numerous fine, scattered areas similar to those noted in the cardiac musculature. These, however, were somewhat lighter in color and had the appearance of minute infarctions. The cortex was not reduced in thickness. The pyramids did not share in the areas of discoloration. The left ureter appeared normal. The right kidney measured  $11 \times 6 \times 4$  centimeters and weighed 160 grams. Its appearance was in every respect identical with that of the left side.

The abdominal aorta showed no gross evidence of syphilis. The iliac vessels and ascending vena cava were negative. The lymph vessels in the abdominal cavity were not distended. The retroperitoneal lymph nodes appeared hyperplastic.

The submucosa of the rectum showed several areas of hemorrhage in the form of small, brown, raised spots. The mucosa was somewhat congested.

The bladder mucosa showed many rounded, elevated brown areas which felt firm and were free of ulcerations. They were scattered throughout the mucosa but most abundant at the trigone. The urethra was normal.

The vagina and vulvae were normal in appearance, the uterus normal in size and position. The tubes appeared normal and patent. There was a small cyst in the left ovary. The right ovary appeared normal.

Sections of skin were removed from various parts for microscopical examination.

The left knee joint was opened by a semilunar incision. The joint appeared pale. The cartilages showed no gross change. A piece of the synovial membrane and a section of the joint surface of the femur were removed for microscopic examination. At the time of autopsy the following gross pathological diagnoses were made:

**Scleroderma.** Extreme generalized arteriosclerosis with multiple minute infarcts of the heart muscle and kidneys. Cardiac fail-

ure with hydropericardium, bilateral hydrothorax and ascites. Atelectasis of the lower lobes of both lungs. Congestion and edema of the right lung (base). Petechial hemorrhages, recent and old, in the mucosa of the bladder and rectum. Atrophic arthritis of the left knee. Multiple decubital ulcers.

The *Microscopical Findings* were as follows. The *spinal cord* showed congestion and edema and early post mortem changes. There was no tract degeneration and there were no changes in the meninges. The *heart* showed marked subepicardial fatty infiltration with serous atrophy. There was atrophy of the heart muscle, with areas of increased stroma and fatty degenerative infiltration. The larger coronaries showed a well advanced sclerosis. There was sclerosis of the endocardium. The *aorta* showed a well advanced sclerosis without lipoidosis. There was no evidence of syphilis. The *lungs* showed marked congestion and edema and a chronic passive congestion with an acute exacerbation. There were numerous heart lesion cells. There were patches of early pneumonia and atelectasis. The *bronchial nodes* were heavily pigmented and markedly congested but free of tubercles. The *larynx* showed a chronic edema. The *thyroid* showed excessive colloid (colloid goiter) and increased stroma. There was no lymphoid hyperplasia. The *fat* stains showed a small amount of lipoidosis. The *spleen* showed chronic passive congestion, atrophy and relative increase of stroma. The *colon* showed chronic catarrh. The *appendix* showed old fibrosis and chronic catarrh. The *small intestine* showed atrophy and congestion. The *stomach* showed post mortem changes, marked atrophy and slight congestion. The *pancreas* showed slight atrophy and chronic passive congestion. The *liver* showed chronic passive congestion, atrophy, fatty infiltration and localized angioma cavernosum. The *fat* stains showed marked fatty infiltration. The *gall bladder* was negative. The *adrenals* showed a patchy lipoidosis but no infiltrations. The *peri-adrenal fat* showed serious atrophy and inflammatory infiltration. The *kidneys* showed an acute progressive infarction of the outer portion of the cortex with arteriosclerotic atrophy. There was



a chronic parenchymatous degenerative nephritis. The *lymph nodes* showed a chronic hyperplastic lymphadenitis. Chronic sinus catarrh. The *paravertebral ganglia* showed no changes. The diaphragm was negative. The *vertebrae* showed a moderately hyperplastic marrow. The *knee joint* was markedly atrophic, the bones osteoporotic and showing an absence of red marrow. The *skin* showed a very marked melanosis of the rete. There were numerous chromatophores in the corium. There was a diffuse sclerosis of the corium and subcutaneous tissues. There was atrophy of fat tissue and replacement by a dense, hyaline connective tissue. Scleroderma. *Striped muscles* were markedly atrophic, with interstitial fibrosis. The *urinary bladder* showed marked fibrosis of the submucosa. There were numerous cell nests of Brunn and a definite sclerosis of the submucosa. The *vagina* showed marked fibrosis of the wall. The *uterus* showed atrophy, the cervix dense fibrosis and a papillomatous hyperplasia of the squamous epithelium; also old glandular erosion. The *Fallopian tubes* showed old fibrosis. The *ovaries* showed marked fibrosis and atrophy, an unresolved corpus luteum in the left ovary.

*Final Pathological Diagnosis* Scleroderma. Chronic atrophic arthritis, most marked in the knee and elbow joints. Advanced sclerosis of aorta and renal arterioles. Progressive infarction of the kidneys. Cardiac insufficiency. Hydropericardium, bilateral hydrothorax and ascites. Fatty liver. Lipoidosis of the kidneys. Early lobular pneumonia. Chronic hypertrophic cystitis with cell nests of Brunn and marked sclerosis of the submucosa. Chronic fibroid vaginitis. Cervical erosion. Large petechial hemorrhages in the bladder and rectum. Multiple decubital ulcers. Hemangioma cavernosum of the liver.

### SUMMARY

The physical and autopsy findings of a case of scleroderma are reported. The local changes in the skin conform in all respects to those previously re-

ported by other observers. They consist essentially of a fibrosis with hyalinization, with secondary atrophy of skin structures, with pigmentation. The striped muscles showed marked atrophy.

The patient presented moderate changes (fibrosis) in the thyroid and slight inflammatory and lipid changes of the adrenals. These changes are so common without scleroderma that they can hardly be taken as evidence favoring the endocrinal origin of the condition.

The widespread fibrosis and sclerosis shown by this case in organs other than the skin might be interpreted as indicating some change in the general metabolism allied to gout. As writers have begun to characterize generalized xanthoma as evidence of a "lipoid gout" so *scleroderma* might be styled a "sclerotic" or "fibroid" gout in distinction to the ordinary "calcareous" or "urate" gout. Strength is given to the assumption by the fact that cases have been reported showing the coincident association of scleroderma and calcareous gout in the same individual. Numerous cases have been reported of scleroderma with calcareous concretions in the skin and subcutaneous tissues. There exists a whole series of affections of complex origin varying from trophic conditions of the skin associated with calcareous concretions to scleroderma. In the present case no lime-salt deposits were present, otherwise the hyalinization of the connective tissues is precisely the same as that seen in cases of scleroderma with nodular subcutaneous calcifications. Since the cases of scleroderma showing lime-salt concretions have been explained

on the basis of a phosphoremia under the influence of a functional disturbance of the endocrine system, those without calcification must apparently lack the calcifying factor of the dyscrasia. The process of lime-salt infiltration is a terminal stage, which appears only in certain cases, and in these

only in certain zones. It is apparent that this whole series of conditions must be etiologically related, that they must represent the same metabolic and dysendocrinal background with a varying humoral factor, a lipodemia in certain cases, in others a calcemia or phosphaturremia, in others a uricemia

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# The Management of Some of the More Common Diseases of the Lower Bowel

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**D**ISEASES of the anus and rectum are the most neglected of all the pathologic conditions affecting the human organism. Just why this is true is difficult to explain. Both women and men have an inherent reluctance in volunteering information concerning abnormal conditions about the anus. They frequently use the various advertised nostrums to treat themselves, rather than seek medical advice. The medical profession has not considered seriously enough its responsibility in caring for the diseases of the lower bowel. Medical instructors casually mention anorectal diseases and medical journals are conspicuously short of articles bearing on this subject. Physicians often neglect to question their patients concerning symptoms which would lead to a proctoscopic examination. The busy physician will frequently prescribe an ointment or suppositories without making a rectal examination. Needless to say the results of such treatment are far from satisfactory.

The lower bowel is as accessible for examination as the nose and throat. Preliminary preparation by a simple enema is usually satisfactory. If a proctoscopic table is not available, the

patient can be examined in the knee-shoulder position on an ordinary table. The instruments necessary are a medium size sigmoidoscope and anoscope with direct light, finger cots, microscopic slides, and cotton swabs on long applicators. Where a water faucet is available, a long tube suction outfit can be used with advantage.

Indications for proctoscopy are pain in or about the rectum or anus, bleeding from the anus, protrusions, pruritus, abnormal discharge, crawling sensation in the anus, and unexplained diarrhea or constipation. If every patient is questioned concerning these symptoms, it is surprising how many will acknowledge one or more being present. Examination of the anus should be made with the patient lying on the side with the knees flexed. In this position the sphincters are relaxed and very little pain is experienced. If the patient is allowed to strain as at stool, abnormal conditions such as fissures, and enlarged papillae, are brought into view. In the same manner also, internal hemorrhoids or polypi, are forced to protrude and can be seen. The examining finger should be inserted and by a rotary movement the anus and lower rectum carefully

palpated After this examination the patient can be placed in the knee-shoulder position and proctoscopy performed

Constipation is frequently the result of pathology in the lower bowel Any condition which results in abnormal sphincteric contraction at the anus will eventually produce constipation or fecal impaction. Errors in habit, diet and sedentary living are productive of stasis in the colon Hard dry fecal masses accumulating in the rectum produce an atony of the bowel wall and irritate the structures comprising the anus Small fecaliths entering the crypts of Morgagni cause a chronic inflammation and subsequent abscess formation Anal papillae become hypertrophied by irritation and the elongated papillae produce a contraction of the sphincters of the rectum Engorgement of the hemorrhoidal plexus frequently results in hemorrhoids When the anal mucosa is irritated and injured by hard feces, fissures are formed The acrid discharge from infections involving the papillae, crypts and fissures, pours over the skin around the anus causing a pruritus Therefore patients with any of the above diseases may seek medical advice because of pruritus ani

Diarrhea, unless profuse or frequent, is often ignored by the patient and physician Intermittent loose stools may be due to errors in diet, achylia, chronic cholecystitis, protozoan infection, chronic colitis, proctitis or polyposis Amebiasis is not uncommonly found in patients who have no diarrhea Frequent watery stools accompanied by tenesmus is the most common cause of hemorrhoids Stool ex-

amination should be made of every patient complaining of diarrhea

Pruritus ani is fairly common and is a complication of some disease higher up in the bowel Ointments and powders applied naturally give only temporary relief unless the cause is found and relieved Every patient complaining of pruritus ani should have a careful examination of the anus and rectum

Papillitis is hypertrophy of the anal papillae due to chronic irritation These papillae may become enormously enlarged and protrude through the anus giving rise to a crawling sensation which is sometimes mistaken for worms

Cryptitis usually accompanies papillitis The crypts of Morgagni secrete the mucus which lubricates the feces in its passage through the anus When they become infected, they expel an acrid fluid which is largely responsible for pruritus When the infection in the crypts burrows through the mucosa, local abscesses form which may penetrate the perianal and perirectal spaces, producing large deep seated abscesses and subsequent fistulae Cryptitis is a focus of infection which is frequently overlooked There is an abundant blood supply to the anus and absorption of pus from this source can produce focal symptoms as easily as infected tonsils or septic teeth One of our patients, a girl 22 years of age, had complained of progressive weakness, loss of weight and a daily rise of fever for four years Frequent general examinations had been made by various physicians with negative findings. Her lungs were normal, her urine contained no pus and

her tonsils had been removed without relief. On careful questioning, she remembered on a few occasions to have noticed an itching and burning in the anus and a few times her underclothes were stained yellow. On anoscopic examination a large infected fissure and abscess of the post-anal crypts were found. There is no doubt of this being the focus which had previously been overlooked.

Fissure in ano with its sentinel pile, is a familiar picture to all. Text books tell us that ninety per cent are found in the posterior anal commissure. We have found almost as many anteriorly. Superficial fissures in the anal skin are often multiple. Deep fissures into the mucosa are usually single. Pain in the rectum during and after defecation is the outstanding symptom. If the fissure is deep enough to expose a nerve filament or sphincter muscle, the pain may be severe enough to require an opiate. Fresh bleeding after defecation always occurs when the fissure involves the anal mucosa. Patients with long standing fissures become anemic and the general health is impaired. Pruritus ani develops when the fissure becomes infected. The purulent discharge excoriates the skin around the anus producing a constant irritation which is impossible to control without correcting the fissure.

Peri-rectal abscesses are common. Infection from the crypts and fissures burrows through the mucosa above Hilton's white line and entering the peri-rectal spaces, finds a fertile field for abscess formation. The symptoms of a peri-rectal abscess are, pain in or around the rectum, extreme sensitiveness, fever, rigors and leucocytosis.

Unless the abscess is drained early, it will penetrate the soft structures along the line of least resistance, pointing into the rectum, vagina or into the buttock on either side of the anal opening. If such an abscess is opened early much destruction of tissue is prevented. Fistulae usually result from these abscesses. Correction of fissures, cryptitis and constipation will greatly reduce the number of peri-rectal abscesses.

Fistula in ano is an infected tract through the soft structures of the buttocks or perineum, resulting from an incomplete healing of an old abscess. If the infection has burrowed in several directions the openings will be multiple. A blind fistula has only one opening. A complete fistula drains into a viscus and externally in the buttocks or perineum. Fistulous openings are quite characteristic. There is an eversion of the subcutaneous tissue, forming a teat-like elevation with an opening in the center from which a purulent material can be squeezed. Blind fistulae pointing into the rectum are often difficult to locate. One can often palpate the indurated area around the opening by the examining finger. A direct view through the anoscope reveals the sinus and makes the diagnosis certain. The vast majority of fistulae are not tuberculous though fistulous tracts are frequent in patients with pulmonary tuberculosis.

Hemorrhoids, both internal and external, are the result of mechanical pressure upon or irritation of the hemorrhoidal plexus. The mechanical pressure by the pregnant uterus and the straining during childbirth frequently

result in large internal hemorrhoids. Constipation, fecal impaction, and diarrhea from disease or purgation cause a chronic congestion of the veins of the lower rectum and subsequent varicosity. Internal hemorrhoids are covered with mucus membrane and originate above the internal sphincter. They may protrude en masse forming the well known grape-like cluster and become very painful. This variety frequently bleeds profusely and if untreated will cause a partial prolapse of the rectum. When contraction of the internal sphincter cuts off the return circulation, strangulation occurs. This condition is very painful and demands emergency treatment. External hemorrhoids are covered by skin, having their origin below Hilton's white line. A large external hemorrhoid may become thrombosed causing acute pain and swelling.

In making the examination for hemorrhoids, the patient should be placed on his side with the knees flexed on the abdomen. The buttocks are separated and he is asked to strain as at stool. The hemorrhoids will present at the anal opening. The gloved index finger well lubricated is gently inserted and careful palpation with a circular movement made to determine the extent of the hemorrhoids. Later, the patient can be examined through the anoscope in the knee-shoulder position.

**Polypus** Polypi may be found singly or in large groups and will be found complicating other rectal diseases. The usual location of a single tumor is in the lower rectum about two inches from the anus. It sometimes grows on a long pedicle and may protrude

outside the anal opening. Multiple polypi may fill the entire colon and cause few symptoms. The usual symptoms are abnormal protrusion, bleeding, diarrhea, and partial obstruction. Polypi are usually benign though they may undergo malignant degeneration. They are more often found in young people.

Strictures of the rectum are the result of previous inflammation. All of the cases have their origin in some previous intra-rectal injury, or irritation due to dysentery, carcinoma, syphilis, tuberculosis or muscular spasm. The symptoms are those of obstruction due to the narrowing of the anal canal. The stools will be soft, small, thin and contain mucus and sometimes blood. Gaseous distension from incomplete evacuation, vague pains in the pelvis or back and general malaise from auto-intoxication. Syphilitic strictures are far more common in women than in men.

**Malignancy** Cancer occurs in the rectum more commonly than in any other part of the colon. The favorite sites are the lower dilated portion or ampulla and the rectosigmoid. Ulceration occurs early. The onset is insidious with no loss of weight or cachexia in the beginning but rapid loss in the late stage. There is often a sensation of weight and pressure in the rectum accompanied by alternate diarrhea and constipation. The stools are blood stained when ulceration has occurred. Where the cancer is located in the ampulla, it can be palpated by the examining finger. In the rectosigmoid it can be seen through the proctoscope. Malignancy of the rectum is more common in men than in

women A characteristic feature about it is that it often occurs in individuals under thirty years of age Metastasis occurs by way of the lymphatics and veins The diagnosis is made by the symptoms, the examining finger when in the ampulla, the proctoscope when higher up in the rectum and by the deformity seen in an opaque enema Patients in the cancer age who complain of sudden onset of constipation or alternate constipation and diarrhea, who have symptoms of partial obstruction and blood stained stools, should be carefully examined for rectal carcinoma In the end stage when loss of weight and cachexia appear, the condition is usually hopeless because of metastasis having already occurred

Management of the diseases of the anus and rectum Treatment may be divided into three classes

- 1 Prophylactic
- 2 Medical
- 3 Surgical combined with medical

Prophylactic treatment consists of hygienic measures, cleanliness, correction of constipation, diarrhea, the proper mastication of food, the drinking of an abundance of water, and the avoidance of using unclean nozzles on enema syringes

Medical management is beneficial in simple inflammatory conditions such as cryptitis, papillitis, superficial fissure and mild hemorrhoids We have seen some excellent results from the application of 5% mercurochrome (220 soluble) on cotton swabs, followed by the instillation of two ounces of extract of witch hazel into the rectum Treatments are given every day at

first, then every other day As the condition improves, treatments are given twice weekly until the lesion has healed The instillation of four ounces of olive oil at night or suppositories containing a mild antiseptic such as boric acid, zinc oxid and ichthyol is often a helpful adjunct to the local treatments

Surgical treatment is necessary in all cases of deep seated cryptitis, elongated papillae, deep fissures, prolapsing, strangulated, thrombosed or bleeding hemorrhoids, polypi, abscesses, fistulae and malignancies

It is our custom to follow up all our surgical cases with medical treatment until the wounds have healed Convalescence is shortened, the wounds heal more kindly, the patient is more comfortable and the end results are far more satisfactory when this procedure is followed Beginning on the fourth day, when the bowels have moved, we take the patient to the treatment room daily for treatment similar to that outlined under medical management The wounds are cleansed and the dressing changed after each bowel movement and in the case of postoperative fistulae, the iodoform gauze packs are changed daily This requires a great deal of work but the results more than justify the effort expended

In conclusion I wish to emphasize the importance of a careful examination of the lower bowel, in all patients who present symptoms pointing to disease in this region Treatment should continue until healing has occurred In disease of long standing many weeks may be required to restore the bowel to normal function Patients as a rule co-operate well and are grateful for the relief obtained



# Glycosuria and Diabetes

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**A**T the February meeting of the Progressive Medical Society of New York Dr Louis I Harris, Health Commissioner of New York City, called our attention to the significance of the Periodic Health Examinations, emphasizing the importance of age. The usefulness of the periodic health examination can hardly be demonstrated in a more impressive way than in the practical case of glycosuria and diabetes. In this special instance the periodic health examination undoubtedly increases the number of the early diagnosed cases and consequently if there is any value in the early diagnosis, this swings the ratio between the mild and severe, respectively between the early and neglected cases in favor of the frequency of the mild and earlier forms of the disease.

Consensus of opinion, both public and professional, is prone to consider glycosuria and diabetes as synonyms, and as a practical demonstration the life insurance companies find any slight degree of glycosuria, without further analysis of the case, sufficient ground for refusal to issue policies.

Still we safely can say, that both conditions are not identical. presence of dextrose in the urine does not necessarily mean diabetes, just as albuminuria is not identical with nephritis.

There are principal differences between both. While glycosuria is only a symptom—certainly the most important and characteristic for diabetes—which can as a concomitant symptom be encountered in various other morbid conditions too, diabetes is a disease-entity, characterized by a faulty metabolism—not solely, but principally—of the carbohydrates. While most of the glycosurias are innocent, often transitional occurrences, without progressive tendency, diabetes is, even in its mildest form, a persistent disease, which may progress and may, due to its inter-relation with the other organs, affect the entire system.

Contrary to the varying etiology of the various forms of glycosurias, the uniformity of that of diabetes mellitus cases is significant. Diabetes mellitus is actually a true disease-entity. Still, on closer view we may discriminate between the type of diabetes of the young and of older people. This differentiation is more than something attributable to the different ages.

The diabetes of corpulent, over-nourished, elderly people offers a more favorable prognosis than the diabetes of lean children and young adults. But the prognosis is not better because they are stout or overfed. Indeed they develop diabetes because they carry on this mode of living and their over-

indulgence in nourishment predisposes to its development. Moreover, the diabetes of older people is often due to degenerative processes in the vessels, not different in character from those met with in other organs. Diabetes from these causes has an easily determined etiology and accordingly it can easily be combated or improved. It is not always a disease *sui generis*, it is often a condition dependent on overfeeding, like obesity. Surplus of energy in the first instance is shown as sugar in the urine, in the other it leads to an excess of fat. This diabetes is strikingly different from diabetes juvenilis.

Diabetes juvenilis represents a very severe, and before the insulin era an absolutely deadly disease. These young people need energy not only for keeping their equilibrium, they need surplus of energy for their growth as well. But unfortunately these severe diabetics (and that is the reason they are severe) cannot utilize carbohydrates, and this metabolic disturbance, as is well known, secondarily affects the fat metabolism as well. Both impairments combined—since no energy can be furnished to keep up life—make living impossible. They inevitably lose weight since they cannot utilize the calories in their diet. That makes them severely sick, therefore they become more lean. If they could be kept in equilibrium, or if they could gain weight, their life would not be seriously endangered, this would be equivalent to utilization of calories. Fattening is an evidence of cure here—not the aim, but rather a natural effect of improved condition—like

weight-reduction in the diabetes of the obese and of elderly individuals. Of course stout or overfed persons also may develop true, severe diabetes, just as the diabetes of meager persons can also be mild.

In diabetes juvenilis the diabetes is primary, general weakness and under-nutrition are secondary. In diabetes of older individuals, corpulence is primary and diabetes develops consecutively. The importance of obesity as primary factor, in these cases, is also emphasized by Joslin, Mosenthal, etc.

The diabetic, just like a normal man, should have his normal, average weight, the spare should be fattened, the stout should be reduced, not only because an average weight is optimal, but for the sake of combating the ill health which is etiologically important in mild cases of those in later life, or to correct emaciation due to the severity of the disease in diabetes juvenilis.

Weight apposition offers a better prognosis in young people, while reduction in weight should always be aimed at in obese adults. If the constitutional condition seems to have a causative relationship to the development of the disease, the opposite state should always be aimed at.

But even if there is a discrimination in the clinical appearance, prognosis, etc., between both forms, the faulty metabolic disturbance is in all these cases identical, only quantitatively different.

Diabetes mellitus is characterized by a faulty mechanism not only of the carbohydrate, but also of the fat and protein metabolism. The anomaly of the carbohydrate metabolism should

not be dwelt upon. It is too well known. None the less important are the fatty metabolic disturbances, which are, as a rule, encountered only in the more severe cases. It is not important from this point of view, whether or not this is the case because the fat burns only in the flame of the carbohydrates, as stated by Rosenfeld and as recently experimentally proven by Shaffer, and accordingly as long as the carbohydrates are properly utilized, no change in the fatty metabolism occurs, or perhaps because a partial or incipient change in the pancreas affects only the carbohydrate metabolism, and farther advanced alterations can bring on changes in the katabolism of the fats only. The fact is, that the danger connected with diabetes was and still is, more to be seen in the metabolic disturbance of the fat, than in that of the carbohydrates. Acetone, diabetic acid and beta-oxy-butyric acid, the scourge to diabetes, are representing the intermediary products of the fatty metabolism, indicating that the fatty acids cannot be oxidized to their end-products.

Not all the fats, only those with even number of C atom endanger the system with the formation of the beta-oxy-butyric acid. Max Kahn's interview, a synthetic fat with odd number of C atom should even by a severe diabetic be broken down to its end-products to  $H_2O + CO_2$ , without forming aceton-bodies. Louis C Johnson calls incomplete oxidation of the fatty acids ketosis, and if these substances accumulate faster than they can be excreted, we have acidosis or

diminished bicarbonate of the blood. The degree of acidosis can be measured either directly by the determination of the actual amount of the aceton-bodies or indirectly by estimating the amount of the alkaline reserve of the blood plasma, by determining its  $CO_2$  combining power.

In case of insufficient glucose-oxidation the decomposition of the fats is incomplete. It is assumed that the oxidation of one molecule glucose suffices to completely oxidize 1 molecule fatty acid. Furthermore incomplete breaking down of 1 molecule fatty acid will produce one molecule ketone body. According to P. A. Shaffer and Wilder, if the molecule of fat to be burned is two or more times larger than the molecules of the actually burned carbohydrates (from this standpoint it is unimportant whether the carbohydrates are not ingested as in starvation, or not utilized as in diabetes), the katabolism of the fat stops at the intermediary stage of the aceton-bodies. According to Woodyatt, a safe ketogenetic anti-ketogenetic ratio, i.e.  $FA/G$  is 1.5 or less, in other words  $\frac{0.46 P + 0.90 F}{C + 0.58 P + 0.10 F}$  should be 1.5 or less, being the source of F, C, P, exogenous or endogenous, or F should not exceed  $2 C + \frac{P}{2}$  especially with diets of magnitudes above the basal caloric requirement, because the surplus of calories will—at the same body weight—increase the acidosis concentration, i.e.  $\frac{(\text{aceton bodies})}{\text{kg}}$  ratio.

The lipid changes in the blood

serum, and the increase of its cholesterol content as manifestations of the fatty metabolic disturbances should only be mentioned here

The knowledge of the metabolic disturbances of the proteins in diabetes mellitus is generally less known. Since, during the decomposition of the proteins in severest experimental phlorizin diabetes we find the amount of dextrose 3.65 times higher than that of the nitrogen (1 gm of N being derived from 6.25 gms of protein) as expressed by the D/N ratio, it can be easily calculated that the dextrose production from protein amounts to its 58% by weight. In other words the proteins during their metabolism split off 58% amino-acids, convertible into glucose, with antiketogenetic effect.

Since a long time it has been known to the clinicians that some of the diabetics, the so-called protein-sensitive diabetics, do not tolerate the proteins very well, i.e. these diabetics respond to the increase of the protein in the diet with the prompt rise of glycosuria. Each case behaved somewhat differently, and each case separately had to be tried out for its protein-sensitivity.

Outside of this, there is also another type of metabolic disturbance of the proteins, which is more analogous to, but independent from those of the carbohydrates and fats. I found fifteen years ago, with my co-worker Dr. B. Tausz, that the urine in most of the cases of severe diabetes mellitus contained increased amount of amino-acids.

Amino-acids are as well known hydrolytic products of the proteins

through the intermediary stage of meta-proteins, proteoses, peptones, polypeptids. But as according to Lengyel and Hary, during the fermentation-reactions of the decomposed proteins in the stomach, no heat-production will be observed, hyperamino-suria means from energetical view-point total loss of the respective proteins.

The hyperamino-suria found in our cases was an absolute, a relative and an alimentary one, pointing to the insufficient utilization of the proteins. Hyperamino-suria had after all kindred significance and was analogous to the acidosis due to the insufficiency of the fatty metabolic changes.

We soon completed our work by the complementary experimental part, and found hyperamino-suria in pancreas-diabetes of dogs, i.e., after preliminary pancreas extirpation had been performed. The hyperamino-suria is caused only by the loss of the internal secretion of the pancreas, because ligation of both of the pancreatic ducts had no effect upon the degree of the excretion of the amino-acids.

The findings of the diabetic hyperamino-suria were soon corroborated by a number of authors (among them M. Labbe and H. Bith; H. Labbe, Pribram and J. Loewy, W. Loeffler, etc.).

Accordingly the protein metabolism suffers, partly because its decomposition may stop at the stage of amino-acids, and partly because another large amount of amino-acids enhances through its antiketogenetic effect the sugar-excretion, acting similarly to dextrose.

The glycosurias have a varying eti-

ology and pathology, and accordingly their interpretation and significance cannot be uniform. The best studied form of the non-diabetic glycosurias is the clinically known renal diabetes, and the phlorizin glycosuria, which is often considered the experimental form of the renal diabetes.

Outside of these forms there are other types of the non-diabetic glycosurias, as those after shock, trauma, cerebral hemorrhage, commotion of the brain, injury, experimental pique, in asphyxia, narcosis, infectious and post-infectious conditions, arterial hypertension, chronic nephritic conditions, imbalance of the internal secretory organs, as the primary and compensatory hyperfunction of the thyroid, adrenals, hypophysis, or administration of their active principles as that of the adrenalin, hypophysis extract, thyroxin, etc., to give only an idea as to the multitude and heterogeneity of these forms.

If we want to make a differentiation between glycosurias of any origin and diabetes mellitus, of any severity, the following questions should be cleared up

- (1) Presence or absence of reducing substance in urine;
- (2) In case of its presence, identification of its dextrose nature;
- (3) Functional urine test with 50 or 100 gms. of dextrose
- (4) Blood-sugar determination on fasting.
- (5) Sugar tolerance curve, i.e., blood-sugar estimation before, and 1-2-4 hours after the ingestion of 50 or 100 gms. dextrose (last 2 requirements only if feasible).

As an explanation to the 3rd requirement The urine should be collected and examined 2 hours after the ingestion of about 100 gms of sugar or somewhat more other carbohydrates, taken in a convenient way, in form of a breakfast, as a functional test meal.

If this functional test is done in cases of diabetes mellitus, the amount of the dextrose in the urine increases considerably. If any other form of glycosuria is present, with the chief representative of the renal type of glycosurias, the small amount of glycosuria which was present in the urine on fasting, or at any time during the examination, will, as a rule, stay as it was or even as the case very often is, decrease or disappear.

In my judgment this is the most simple, practical and rational test for differentiation

As an explanation to the 5th requirement, when instead of the blood-sugar curve, only one determination can be taken, the most important examination is the one taken 2 hours after the ingestion of glucose. The blood-sugar value after the ingestion of glucose returns within 2 hours to normal figures, respectively to the figures found before the test meal was taken. This is the case under physiological and also under most of the pathological conditions. We count in this latter group also the various glycosurias. In true diabetes mellitus not only the height of the blood-sugar level is raised compared with those under normal conditions, but, and this seems to be the most characteristic feature, the return to normalcy never occurs.

within 2 hours, the delay may take a much longer period of time due to, and in accordance, with the severity, of the individual case. But, like glycosuria, also hyperglycemia, or even a positive sugar tolerance test alone cannot be considered as absolutely proving the existence of a true diabetes mellitus, as emphasized also by Mosenthal

There are different aberrations, referring to or characterizing certain parts of this mechanism. Hugh McLean calls "lag" cases, in which the blood-sugar level surpassing the physiological threshold value returns within 2 hours to normalcy. The elevation of the blood-sugar level above the physiological threshold value brings on glycosuria, which, however, disappears within 2 hours after the ingestion of the carbohydrates.

Aside from the lowered renal threshold value, its increase also deserves our attention. The increased renal threshold value is encountered in the far advanced cases of chronic diabetes mellitus, and also in those combined with chronic nephritic conditions. Sometimes there is no such basic disease to be found and if the increase of the threshold goes beyond certain limits, the glycosuria may be entirely missed in the simultaneous presence of hyperglycemia. Polyuria and polydipsia may mask the diabetes mellitus and mislead to the erroneous diagnosis of diabetes insipidus, as long as the hyperglycemia does not clear up the nature of the situation, namely, the inhibitory function of the sugar-excretion, in other words diabetes mellitus with increased renal threshold value

for glucose, as in one case observed by R. Balint

J. Andresen and A. Schmidt describe high degrees of hyperglycemia without glycosuria in different infectious diseases, so e.g. in typhoid fever, dysentery and especially in scarlet fever, where they found blood-sugar values around 0.3% (without glycosuria) in contrast to measles, in which disease normal glycemia seems to be characteristic.

It is well to remember and this cannot be emphasized enough, as we find it accentuated in v. Noorden's works, that the mild and especially the incipient cases of diabetes mellitus may vary to a great extent, and that there are diabetes mellitus cases in their earliest stage similar to those diagnosed as diabetes renalis.

Not only the different forms of glycosurias are etiologically and pathologically different, but its chief representative, the diabetes renalis, is, even today, according to different authors, interpreted in entirely different ways.

In my opinion, diabetes renalis is principally different from diabetes mellitus, notwithstanding the fact that the differentiation can—especially in the earliest manifestation of the disease—be sometimes difficult or not even possible. As a rule, in diabetes mellitus, the diabetes is persistent even if the glycosuria is not (as in the mild cases), while in renal diabetes the glycosuria is persistent even if the diabetes, i.e., the disease is not (as in the transitional cases).

In renal diabetes, we expect a persistent glycosuria, i.e., any portion of the urine contains dextrose, regardless

of food taking, the glycosuria is with very few exceptions, mild, the dextrose concentration varying between 0.1-0.5%. The persistency of glycosuria is very characteristic, and this should be emphasized as against the mild cases of diabetes mellitus, in which latter case aglycosuria always can easily and within a day or so be achieved. In renal diabetes the small amount of dextrose, often only traces, will no matter how strict carbohydrate-free diet is given, persist. Lewis and Mosenthal observed only after a six days' lasting starvation, disappearance of the glycosuria. A slight degree of stubbornly persistent glycosuria, independent of food-taking, is the most significant feature of the diabetes renalis.

The diagnosis of renal diabetes is never complete without blood-sugar determination. The blood-sugar is always low, normal, low-normal or sub-normal, this is the case, not only on fasting, but also after administering a great amount of carbohydrates. The physiological renal threshold value for glucose is never surpassed, and still there is a continuous glycosuria. The glycosuria is always independent of the height of the blood-sugar level. There is no response between carbohydrate intake and the degree of glycosuria, but if there is any, as it sometimes may occur, we find the interesting reverse type, on increasing the carbohydrates in food the degree of glycosuria may lower. Gibson and Larimer found that in renal diabetes the injection of 50 gms. of glucose lowered the glycemia to such an ex-

tent that hypoglycemic reaction may appear.

Although most cases of renal diabetes are mild, there does not exist any principal reason why occasionally a higher degree of glycosuria could not be met with. And actually, there are a few cases published in the literature with considerable severity. Out of the 3 cases of renal diabetes published by me within the last 15 years, the first one referred to a very severe case with a high degree of acidosis.

In this latter case I was able to show, that although the case otherwise proved to be a classical form of renal diabetes, its severity differed in no way from very severe cases of diabetes mellitus. The daily loss through dextrose excretion amounted to values around 150-200 gms, and the degree of acidosis was also remarkable. In this case, the first in the literature, R and Q determinations were performed and it was found that the same was very low, 0.709, just as in cases of severe diabetes mellitus, and it did not even after the ingestion of 150 gms of dextrose show any increase.

Contrary to the continuity of the glycosuria in renal diabetes, the sugar excretion in mild diabetes mellitus is intermittent. In these cases the elimination of the dextrose is not a continuous process, it greatly depends on the carbohydrate content of the food ingested within the last few hours. In the mildest cases of diabetes mellitus when the twenty-four hour urine is free of sugar, the sample voided 2 hours or still more so 45-75 minutes after the carbohydrate containing meals, may contain dextrose in suffi-

cient concentration for its recognition. Therefore, in cases of mildest or questionable diabetes mellitus the two hour sample should be examined. This is the test for the detection of the post-cenal temporary glycosuria.

This question brings up the problem of the carbohydrate tolerance, which used to be stated for twenty-four hours. Instead of this, I have recommended expressing at the same time the tolerance for the single meals too, because if the patient can utilize for instance 75 gms of carbohydrates taken at one meal, he can tolerate 150 gms of carbohydrates when he takes one-half of this amount twice daily, 225 gms, when he takes one-third the amount three times daily.

The knowledge of the post-cenal temporary glycosuria is important also from the standpoint of the maintenance diet. On the preliminary test diet we are slowly, progressively increasing the daily amount of dextrose, on an otherwise isocaloric diet until the first dextrose appears in the urine. This is expressed as the tolerance for sugar. More important, because more sensitive than this test is the examination for dextrose utilization. This limit is reached the moment the dextrose ingested cannot be utilized totally, and it starts, before glycosuria sets in, to raise the dextrose level in the blood. Rise of the blood-sugar level within the renal threshold value is as I found practically coincident in time with the temporary post-cenal glycosuria, i.e., when the 24-hour urine is free of sugar, but the sample voided 2 hours or especially 45-75 minutes after the meal, contains some dex-

trose. This is the period between the utilization and tolerance. In other words, if we want to put the patient on a maintenance diet (the carbohydrates being divided equally into 3 parts) the maintenance diet should precede the diet upon which the first post-cenal temporary glycosuria was observed.

The striking respiratory findings in renal diabetes opened the field to further study in which I was able to show with my co-worker, Dr. E. Schull, that in the experimental phloridzin diabetes in dogs, the  $R/Q$  was equally low, and that severely phloridzined dogs lost the ability to oxidize dextrose. The severity of the phloridzinisation marked the degree of this inhibitory function. Deprivation of the system from dextrose through glycosuria could not be made responsible for the failing rise in  $R/Q$ , because even if superfluous doses of sugar were ingested or injected, and even if double-sided nephrectomy was performed, which stopped the glycosuria at once, the inability to burn sugar, was uniformly present in our cases.

This important fact, namely the lost power of combustion of dextrose in phloridzin poisoning, is able to throw quite a new light on the pathogenesis of the different glycosurias. This holds true, even if met with the disfavor of an author like von Noorden, who, although he could not present any positive arguments against it, yet in his criticism disclosed nothing but aversion to some new facts which might have compelled him to formulate ideas for the explanation of the glycosurias in a different way from that which he had done previously. He



found our results so striking, however, that he felt impelled to write in his book as follows.

"Nun hat mit den gleichen Methoden, mittels derer man jene Theorie stuetzt, den Stoffwechsel beim akuten Phloridzindiabetes untersucht (A Galambos und E Schill) Man kam zum gleichen Resultat scheinbar findet kein Verbrauch von Zucker im maximalen Phloridzindiabetes statt Das hätte doch ein Warnungssignal sein sollen, man hätte sich sagen sollen, dass eben die Methode (Messung des respiratorischen Quotienten nach Kohlenhydratzufuhr, Kap. IV), nicht das beweist, was man von ihr erwartet. Aber die Autoren haben sich nicht einmal die Mühe gegeben, sich mit den Einwänden auseinanderzusetzen, die ich schon vor Jahren gegen diese Methode erhob Wie in aller Welt wollen sie erklären dass durch die Phloridzinvergiftung auf einmal, fast von einer Stunde zur anderem, ein Grundgesetz der Biologie, der Zuckerverbrauch, in den Geweben unterbrochen werden und nach wenigen Stunden, wenn das Phloridzin ausgeschieden ist, wieder voll in Kraft treten soll? Wäre es nicht richtiger gewesen, angesichts solcher ungeheuerlichen Folgerung an der Beweiskraft der Methode zu zweifeln und auch ihre Beweiskraft fuer die Zustände im Diabetes in Frage zu ziehen?"

Noorden's objections to this new fact seem to be nullified by the work of Lusk and Nash and Benedict who are unanimous in corroborating the fact first discovered by us.

Ringer found that 75 gms of glucose given to a phloridzinized dog is

completely eliminated in the urine Lusk stated that the ingestion of this large quantity of sugar in no way affects the respiratory quotient He writes "It is therefore evident that the completely phloridzinized dog has lost the power of oxidizing glucose" Stanley Benedict administered glucose to phloridzinized dogs in an amount sufficient to cause the blood-sugar to rise above the normal, but a rise of  $RQ$  did not occur, showing that sugar is present in ample concentration though it remains chemically untouched

M Ringer says "A completely phloridzinized animal suffers from two essential incapacities. One is the inability to utilize sugar, from which defect follows the familiar train of pathological findings that constitute the picture of true diabetes This is well established. The other defect relates to the inability of the kidneys to re-sorb the sugar (they filter from the blood), resulting in a persistent glycosuria and the hypoglycemia, which distinguishes phloridzin diabetes from pancreatic diabetes This much lowered renal threshold for sugar has somewhat confused the essential diabetic character of the phloridzin injury Indeed it is held in many quarters that the failure of the phloridzinized body to metabolize glucose is due to the subnormal blood-sugar induced by the kidney leak One cannot drink water from a sieve Recently, Nash and Benedict have put the quietus on this view by giving glucose in sufficient amounts to induce protracted hyperglycemia in phloridzinized dogs and recovered it quantitatively in the urine

That phloridzin produces a real lesion of the sugar-burning mechanism, can no longer be held problematic"

Unfortunately, it escaped the attention of Lusk, Benedict, Ringer, etc., that this new fact of the impairment of the oxidizability for dextrose in phloridzin glycosuria was discovered by A. Galambos and E. Schill, who published their experiments in this line in the *Zeitschrift fuer experimentelle Pathologie und Therapie* in 1914. But this is a question of priority only and as such is of secondary importance, and does not touch the main point—the fact as detailed above. Lusk, Nash, and Benedict, also their predecessors, the pioneers, Reilly, Nolan and Lusk, Loewy, Stiles and Lusk, Rosenfeld, etc., gave dextrose per os or subcutaneously to the phloridzined animal and found quantitatively in the urine the amount of glucose ingested, from

this they concluded that this same amount of sugar must have escaped combustion in the tissues. Galambos and Schill are the only investigators who used the method of the respiratory metabolism. By both methods the same conclusions were reached.

The combustibility of dextrose which was considered impaired in severe diabetes, and present in renal or phloridzin glycosuria can after all not serve as a differentiation sign, they uniformly fail in all these conditions, provided the condition has been developed far enough.

After all, renal diabetes can easily and with sufficient accuracy be differentiated from diabetes mellitus. The most characteristic features of these three conditions, grouped respectively according to their resemblances and differences to each other, are summed up in the following table.

	<i>Diabetes Mellitus</i>	<i>Phloridzin Diabetes</i>	<i>Renal Diabetes</i>
Glycosuria	Present	Present	Present
Glycemia.	Increased	Lowered or normal	Lowered or normal
Dextrose threshold of kidneys	Normal Later increased	Lowered	Lowered
Glycosuria after CH intake	Rises	Rises	
Glycosuria after protein intake	May rise	May rise	
Glycosuria after the same diet.	Unchanged	Unchanged	Varying
Glycosuria after CH reduction	May disappear	Present	Present, may rise
Parallelism between blood-sugar and urine sugar concentration	Present more or less	Mostly present	Absent
R. Q. in severe cases	Low	Low	Low
Effect of CH intake on R. Q. in severe cases	Missing	Missing	Missing
Acidosis in severe cases	Present	Present	Present
Dyszoöamylia (lack of storage)	Present	Present	Missing
Response in glycosuria after insulin	Present	Present	Missing
Curative effect of both diet and insulin	Present		Absent

Though there is a great resemblance between these 3 conditions, differentiation is nevertheless important, especially from the view point of the prognosis and therapy

The prognosis of diabetes renalis is in most of the cases good; in severe cases it is less favorable, not only on account of the loss of dextrose through glycosuria, and a possible acidosis, but also because no dietary regulation is effectual, and insulin is of no avail. Fortunately severe cases are very rare

As for the therapy: no dietary regulation is required; insulin is not only inefficient, it is in fact, on account of its blood-sugar reducing effect, dangerous. The low blood-sugar level may easily drop to values causing hypoglycemic reactions. Ineffectiveness of insulin is important not only from the therapeutic, but also from the diagnostic view point.

In diabetes mellitus the therapy consists of administration of a proper diet and insulin

The diet is calorimetrically computed. The basal caloric requirement is determined either on ground of the weight or of the surface area computed with the aid of Du Bois' chart. After deducting the basal protein requirement (P.) which is 2/3 gm per kilogram weight, the balance is supplied by fats and carbohydrates. On computing the amount of the carbohydrates, there are to be considered the carbohydrate tolerance of the patient, the safety relative to the ketogenic-antiketogenic ratio and the total caloric requirement. Simultaneously it should be taken into account whether

reducing or fattening should be accomplished. The remainder of the caloric requirement is supplied by fat. Woodyatt's formula may guide us in our computation. According to this the total amount of glucose should be:

*Basic caloric requirement*

$$G = \frac{\text{Bas. cal requ.}}{17}$$

$$D = G \times \frac{8}{10} - \frac{P}{2}$$

$$F = D \times 2 + \frac{P}{2}$$

Insulin in diabetes mellitus is a causal therapy. The cause of the pancreas diabetes is hypo-isletism, caused by any reason, with or without morbid anatomic or sometimes even microscopic changes, whereby the insulin production is impaired. The insulin administered makes up for this deficiency. Its proper administration equals a cure and should make any dietary regulation superfluous, because it corrects, respectively makes up, for all that is missing. The fact that we are advocating strict dietary regulation proves that insulin treatment is, the way it is administered today, far from being what it should be. Its technic, dosage, administration, etc., is insufficient the way it is used today. The first drawback is explained by its hypodermic administration in doses, and intervals, which do not answer the requirements, because it cannot provide the automatic regulation of the insulin production or of its liberation as it is in the case of normal individuals. If the administration of insulin

would be safe and its utilization automatic, every diabetic should get it, but under the present conditions we administer it only in the severe cases. If under a diet with the basal caloric requirement and the minimum safe amount of carbohydrates no equilibrium in weight, and especially no aglycosuria can be achieved, insulin is indicated.

It is practically not feasible that the blood-sugar reducing effect of the insulin should precisely counteract the blood-sugar increasing effect of the food ingested. If this could mathematically be arranged, no dietary treatment would be necessary. Under-dosage requires dietary regulation, over-dosage brings on hypo-glycemic reaction, which is still more dangerous. This is the Scylla and Charybdis.

Otherwise, insulin is the greatest practical discovery, maybe of this century, the number of lives actually saved goes into ten or hundred thousands. Its effect in coma—and that is the *experimentum crucis*—exceeds the most audacious expectations. No operative activity in any field of surgery can yield more striking results or more sudden changes.

Insulin is the causal therapy in diabetes mellitus as well as in all of its complications.

Few remarks and observations which do not fit themselves to everyday practice with insulin treatment, are

(1) If insulin is not feasible otherwise it may be successfully administered once a day before the chief meal in the evening, the distribution of the

carbohydrates being correspondingly arranged.

(2) The ratio between the number of insulin units and carbohydrate utilization may show a discrepancy, a few units of insulin being able to burn relatively more dextrose than those in larger doses.

(3) Insulin may increase the carbohydrate tolerance during and after treatment. The after-effect enables and in many cases justifies the cyclic administration of insulin for 4 to 8 weeks, followed by a few months of insulin-free treatment.

(4) Insulin may have at a later period markedly less sugar-burning power than earlier, in this way counteracting its tolerance-increasing after-effect.

(5) The same amount of insulin given for a length of time may produce quite a different effect at different stages. An amount which is the proper dose today may be responsible for a hypoglycemic reaction after a few days on an unchanged diet. This implies and necessitates in such cases the gradual decrease of the insulin dose.

(6) Sudden decrease in insulin dose may also cause a hypoglycemic reaction in special instances. Reduction of insulin units may act perhaps by overstimulating the islet-function in the effort to keep up the same insulin concentration in the system as was present before the reduction of the insulin doses started. It may occur that while the insulin doses were being gradually increased, even though large doses of

insulin were administered, aglycosuria could not be achieved, but a few days later, in the period of gradually decreasing doses, aglycosuria set in, and perhaps, even after cessation of the insulin, continued for a certain length of time. Insulin treatment may in such cases resemble the immunization process in some respects.

(7) If we keep the patient on a rather strict diet with nicely adjusted insulin doses, not much carbohydrate accumulation can take place in the system, and the insulin administered will promptly oxidize the carbohydrates available, i.e., the carbohydrates ingested. If we give relatively large doses of insulin with a larger amount of carbohydrates especially if both or either of them are administered in increasing or decreasing doses, postponement, after-effect, accumulation, delayed response, etc., may easily occur; in one case resulting in the insulin assuming some part of the pancreas function, and at a later date in its reduction or cessation overstimulating the arrested islet function; or, the insulin given in excess may deplete the glycogen deposits and the dextrose in the blood and tissues, and, while previously even larger doses did not completely consume the carbohydrates ingested on account of their being engaged in combating the glycogen, the tissue and blood-sugar, after their oxidation the same and even smaller doses applied exclusively for oxidation of the carbohydrates ingested may, with the same carbohydrate intake induce complete aglycosuria or even a hypo-

glycemic reaction, when a few days before even larger doses were unable to do so.

The function of the islets seems—at least to a great extent even in cases of very severe diabetes—only to be suspended, functionally disturbed, and not totally lost. After a rest, due to reduction of the carbohydrates in the food and to a preceding insulin cure, whereby insulin assumes the not entirely lost function of the islets, the latter can and do produce insulin again in an unexpected concentration.

I will not close the topic of the treatment of diabetes mellitus without mentioning the experimental work done by G. Mansfeld who performed a partial Steinach's operation on the pancreas of the dog. He produced after ligation of one of both pancreatic ducts overproduction of insulin, and proliferation, hyperplasia and hypertrophy of the respective Langerhans' islets while the other pancreatic duct remained untouched, carrying the essential and ferments-containing, outer-secretory products, supplied by the intact portion of the pancreas. In case only one pancreatic duct was present he dissected the pancreas into two parts and ligated the one, care being taken for their blood-vessel supply; while the one portion preserved both the external and internal secretion, the other, being deprived of its external secretion, became destined for the prospective hyperplasia or its Langerhans' islands. Whether and how this idea will gain access in the human pathology remains an open question at this time.

# Malaria in Legal Medicine—Cases in Relation With Accidents

By RICARDO AGUILAR, B S, B A, D D S, M D, F A C P,  
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**E**XPERIENCE has taught employers of labor to take into consideration various conditions such as alcoholism, epilepsy, syphilis, diabetes, nephritis, etc., as causes for rejection, particularly in filling positions when danger and responsibility are involved

Any of these conditions may be responsible for temporary aberrations or loss of consciousness, and lead in some instances, to serious loss of life and property

In this connection, malarial infections have not been considered, but as shown by the following case reports may at times be responsible for serious accidents with subsequent medico-legal action and unjustifiable penalties against employers or corporations that are in no way responsible. In many of these cases the individual employees are at fault and not the employer

When an employer presents every known means to an employee to prevent malarial infection, and the necessary agents and instructions for his cure, the former should not be held responsible for the neglect of the latter who does not profit by the instructions given him

In all cases where accidents occur a careful physical examination should be

made of the combination concerned, supplemented by laboratory findings, and a report with a complete diagnosis furnished the Judge in order to enable him to reach a just conclusion and fix responsibility

The proneness of malarial infection to produce delirious and other cerebral conditions whereby consciousness is lost and responsibility ceases, places this disease in a similar category to alcoholism, epilepsy, diabetes, etc. There are two type of cases one is the type in which malaria in an employee to others, is the cause of an accident, and the other is the increase of severity of traumatism in an individual case, on account of malaria infection

*Case No 1—O F native, 19 years old Admitted to Hospital on May 14, 1927 Patient had been with fever for two days Patient was on duty as fireman on a special train and developed suddenly a chill followed by a severe attack of fever In Gualan (a small Railroad Station on the line) the engineer on the train went for lunch, and my patient without any instructions started the engine and ran the train to the next station Fortunately the other members of the train crew succeeded in reaching the engine and it was stopped at the following station. Patient was under arrest but later was brought to Hospital on the authorities finding placed that he had a severe attack of fever This incident*

luckily did not cause accident but it might had been the cause of a serious wreck on the line, as the fireman started without any "via" or orders from the train dispatcher.

On admission temperature was 103, pulse 96, skin pale, with profuse perspiration Tongue coated, liver tender, spleen palpable and tender Patient was delirious Blood was positive for E. A. Malaria parasites

Diagnosis E. A. Malaria (Cerebral Type)

After two days of VIII minims of adrenalin and 15 grains of quinine hypobid temperature became normal and complete relief of symptoms was noted

Case No 2—M. H. native, soldier, 24 years old, admitted to Hospital on July 23, 1928 His right leg was struck by a falling timber while a hurricane swept over a village

Working Diagnosis Compound fracture of right tibia.

On admission patient was extremely prostrated and shocked, with high fever, heart rapid and weak, lungs negative, abdomen slightly distended, right leg undue motility, and severe fractures of both bones, two inches above ankle, showing a site puncture wound of skin, which had bled freely. No evidence of fracture infection.

Diagnosis Compound fracture of right tibia; Clinical Malaria (Cerebral Type)

Patient died on second day after admission and had temperature of 105 and 106 for the two days in Hospital

Case No 3—W. W. American negro, engineman Felt very ill while on engine this morning On arrival at Quirigua left his passenger train engine and reported to Hospital for consultation, and medicine, intending to continue on his engine and finish his run

He was palpably too ill to be trusted on an engine, and he was persuaded to remain in Hospital, and tie up the train until another engineer could be sent to take charge of it.

Patient had been ill for three days and taken treatment outside

Patient vomited shortly after arrival in Hospital, perspired profusely, became nauseated, and went into condition of collapse Severe diarrhea and vomiting supervened

Diagnosis Clinical Malaria (Algid Type)

If this man had continued on his run it is quite probably that an accident might have occurred, giving a medio-legal problem.

# Adrenalin in Malaria

By RICARDO AGUILAR, M D, F A C P, D D S, *Quirigua Hospital,  
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I KNOW of no literature regarding the use of adrenalin in the treatment of pernicious malaria but have noted the beneficial clinical results obtained by Doctor N P Macphail, who has used it rather extensively in cases of persistent nausea and vomiting incident to severe malaria infection

In pernicious attacks, whether of the cerebral, algid or paratyphoid types, sluggish reactions from the use of quinine, intramuscularly, or orally, supplemented by subcutaneous injections of adrenalin chloride in doses of from 8 to 15 minims, it is frequently followed by an acute exacerbation of the symptoms, and though parasites could not be previously found in the peripheral blood, they appeared subsequently in comparatively large numbers, and the sequence of events, in the clinical condition and prompt recovery of the patient was most gratifying

Apparently the adrenal injection caused a constriction of the blood vessels, spleen and other homoiopoetic organs, and forced the parasites into the circulation, relieving pre-existing stasis or loss of vascular tone

Keeping in mind these observations I began to use the adrenalin injections in all cases of pernicious malaria ir-

respective of the type or the localized character of the clinical symptoms and herewith present a few brief cases that will illustrate the prompt results obtained

It may seem curious to the reader to note that in about one half the number of cases reported parasites were not obtained in the peripheral blood. This can be accounted for as follows. In this Division the cases come from the camps which are inspected daily and all those suffering from fever are promptly given quinine in large quantities before they are forwarded to Hospital for treatment. It is well known to all malariologists, accustomed to deal with E A Malaria, that when the parasites are about 18 hours old, they are caught in the deep viscera, and although the peripheral blood may have contained enormous number of parasites when the blood was examined, a smear taken a couple of hours subsequently may fail to reveal parasites or comparatively few may be found

Case No 1—E U (Cerebral Psychopathic Type), native, female, 18 years old, admitted to Hospital on May 1st, 1928

She had complained of severe headache on returning from School, and was seized with a form of cerebral attack, and became delirious, in which condition she entered the Hospital. Temperature was 102,



pulse 120, respiration 24, and she suffered from incontinence of urine. Her blood was positive for E. A. Malaria. For three days the patient was given quinine intramuscularly, 15 grains every 6 hours, supplemented with bromides, without relief. On the fourth day XV grains of quinine administered intramuscularly 20 minutes after an injection of six minims of adrenalin chloride solution in the morning and repeated at noon. Spinal puncture was performed and 20 cc of spinal fluid removed, with a hemolytic solution as though an old clot dissolved in the spinal fluid. Next day the patient was much improved, had been bright, but quinine hypo and adrenalin was given morning and noon, as well as the following day. On the 7th day temperature and pulse were normal, adrenalin and quinine hypos were discontinued and 10 grains of quinine administered orally were given. Patient discharged in good condition on May 15th.

*Case No 2—M N L* native, male, 13 years old, admitted to Hospital May 19, 1928 (Cerebral type). Unconscious and history was not obtainable. Temperature was 104, pulse 144 and respiration 40. Vomiting and delirious. Eyes show nystagmus. Blood was positive for E. A. Malaria parasites and urine showed traces of albumin. Patient was given 10 grains of quinine intramuscularly repeated every six hours and digitalin 1/100 hypo. Hot water bags, blankets, and ice cap to head. Next day patient was still unconscious and temperature was 103¾, pulse 144. Adrenalin minimus V hypo, and 10 grains of quinine intramuscularly morning and night. Spinal puncture was made and 15 cc. of clear transparent spinal fluid removed with normal pressure, but after 15 cc. had been removed, blood appeared in the fluid, which demonstrated that there was acute congestion of the cerebral blood vessels. After the administration of adrenalin and quinine hypodermically, temperature and pulse became normal and complete relief of symptoms were noted. Patient was discharged on May 31st in good condition.

*Case No. 3—F. H* native, male, 30 years old (Cerebral Type). Admitted to Hospital on April 13, 1927, unconscious and history was not obtained. Temperature was 102, pulse 92, respiration 20. Delirious and with nystagmus and positive Kernig. Blood was negative for malaria parasites. Patient was given 22½ grains of quinine hypo twice daily and no relief of symptoms were observed. On the second day seven minims of adrenalin following by 15 grains of quinine hypo were given morning and noon, after which patient became conscious, with normal temperature and pulse. Patient was discharged on the 20th of April in good condition.

*Case No 4—S. R* native, male, 12 years old, (Cerebral type) admitted to Hospital on May 23rd, 1927. Unconscious and history was not obtainable. Temperature was 99, pulse 120, delirious, and blood was negative for malaria parasites. Skin and conjunctivae pale and nystagmus, distended abdomen, enlarged spleen, positive Kernig. Patient was given 5 minims of adrenalin and 7½ grains of quinine hypo. Twice daily for the first and second day with excellent results. On the third day quinine was administered orally. Patient discharged in good condition on May the 1st.

*Case No 5—W C* American negro, 45 year old (Algid Type). Admitted to Hospital on July 19, 1928. Patient had been under treatment for malaria for three days but felt worse the morning of admission. Profuse perspiration, cold skin, profuse diarrhea and vomiting. Admitted to Hospital in a collapsed condition. Temperature was 96, pulse 90 and thready. Blood was negative for malaria parasites and urine showed traces of albumin. Patient was given a minim of adrenalin chloride solution hypo whisky ½ oz every four hours, blankets, hot water bags, etc, followed by 15 grains of quinine intramuscularly on admission, repeated in six hours. Complete relief was noticed in 12 hours, and the following day quinine was administered orally until he was discharged in very good condition on the 29th of July.

*Case No 6*—M R B male, Portuguese, 33 years old Admitted to Hospital on July 22, 1928 Patient had fever and chills, tongue Hepatic and splenic areas tender on pressure Blood was negative for malaria parasites

Patient was under quinine routine combined with plasmochin for six full days running daily temperature of 101 and 102 15 grains of quinine hypo was administered twice daily for two days without any results, until 8 minims of adrenalin and 15 grains of quinine hypos was given Temperature went up to 104, pulse 112 with a crisis of chills, an hour after temperature and pulse were normal and complete relief of symptoms was noted Patient was discharged on August 3rd in good condition

*Case No 7*—F C native, male, 26 years old, admitted to Hospital on May 20, 1927 Patient had fever and chills daily, anorexia, nausea for six days Nutrition poor, skin pale, coated tongue, liver tender at G B region, spleen enlarged and tender Blood was negative for malaria Patient was given 15 grains of quinine hypo twice daily without any relief Eight minims of adrenalin followed by 15 grains of quinine hypo was given twice daily for two days, relieving all symptoms Patient discharged in good condition on May 30th

*Case No 8*—G T native, male, 25 years old, admitted to Hospital on February 26, 1928 Fever and chills daily, headache and nausea for four days Skin pale, jaundice, tongue coated, eyes with jaundiced sclera, hepatic and splenic regions tender on pres-

sure, enlarged spleen, blood negative for malaria, temperature 103, pulse 120

Upon examination on the following day there were E A malaria parasites in his blood Patient had been under quinine treatment for two days without any relief of symptoms, and temperature was still high 8 minims of adrenalin and 15 grains of quinine intramuscularly were administered and relieved all symptoms Patient discharged from Hospital in good condition after six days treatment

*Case No 9*—J C male, native, 17 years old (Cerebral Type) admitted to Hospital on May 23, 1928, in an unconscious condition Skin warm and moist, heart and lungs O K spleen palpable and tender, limbs negative, asthenic and weak, vomiting and delirious Temperature 103, pulse 140, blood positive for E A malaria parasites about 50 per field (thick film) 15 grains of quinine hypo proceeded by 10 minims of adrenalin hypo relieved all symptoms, on the second day temperature was normal This treatment was followed by quinine and plasmochin tablets by mouth Patient discharged in good condition after eight days treatment

Those case reports are representatives of a large number of cases which have been treated in the same manner during the past two years I believe that the use of adrenalin in conjunction with quinine in the treatment of serious cases of malaria deserves further study

# Editorial

## THE FUNCTION OF THE ADRENAL CORTEX

In the higher animals the adrenals consist of two forms of tissue differing widely in their structure, genesis and function, the cortex and the medullary portion. It has been generally accepted that the medulla is the place of production of adrenalin, and that this substance is produced also in other glandular systems closely related to the sympathetic nervous system. But with the acceptance of this fact our knowledge of the general function of the adrenals is exhausted. It would seem logical that the physiology of both tissue complexes must represent an *entity* corresponding to the anatomical concentration of the two tissues. But nothing is known of the function of the cortex. The present day conceptions of the physiologic activity of the cortex fall into three categories. The first of these indicates the rôle of the adrenal as a detoxicating organ. This view is supported experimentally and pathologically by various facts, in part by the occurrence of a susceptibility to poisons of the body in adrenal insufficiency, and in part by adrenal reactions on the appearance of an organ insufficiency or defect resulting from the introduction of poisons into the body. It has been assumed by some workers that the lipoids of the cortex, particularly cholesterol, act as

a kind of neutralizing substance, in the same manner as the last-named precipitates digitonin; by others it is assumed that the poisons circulating in the body fluids are "magaziniert" by the adrenal cortex. The second category is based upon the appearance of the cortical cells under varying conditions. The French School, together with some Russian and German workers hold the view that the essential function of the adrenal cortex is the production of lipoids, particularly cholesterol, for the needs of the body. Against this view is opposed that of the Aschoff School who claim that the adrenal cortex produces neither cholesterol or cholesterol-ester, but on the other hand is simply infiltrated by these substances when they are admitted to the body. This view does not include the denial that the adrenal cortex possesses an up to the present time unknown secretory function. Certain authors holding fast to the idea of the adrenal as a detoxicant organ compromise with regard to the two views given above, in that they believe that the adrenal secretion neutralizes the circulating poisonous material. The third view rests essentially upon the assumption that the adrenal cortex secretes a hormone more or less of general importance to the whole body. Falta and Stephan support this view. Goldzieher, who formerly held the extreme view that the most important

function of the adrenal was that of the medulla, while the cortex was relatively without significance, now believes (1928) that he has isolated a cortical hormone, "nerihormone" with specific action. A hormonal action of cortical extracts had been earlier observed (Kühl, 1926). Further, Goldzieher used rats as his experimental animals, which are the least adapted for the study of the phenomena of cortical insufficiency, since in fifty per cent of these animals accessory adrenal tissue is present, so that it is impossible to be sure that all adrenal cortical tissue is removed in any given case. Alsterberg (1928) has studied the adrenal cortex by means of a new impregnation-method, devised by him. By means of this method he has been able to demonstrate the presence of lipoids in the capillaries of the adrenal cortex which he regards as the true hormonal secretion of the cortex. He concludes that the adrenal cortex secretes as hormone just that lipid substance which enters into the mitochondria of the cells and into all cell structures. The function of the adrenal becomes in this way of general significance, it is a regulator of the activities of the individual cells. While other hormone effects are specific, that of the adrenal cortex is general and difficult to define. Its significance is best shown in the reactions of the different organ-systems in adrenal insufficiency. Destruction of the adrenal cortex leads to death of the animal if accessory tissue consisting of adrenal cortex is not present. Further it is very striking that the temperature regulation is disturbed in great degree and that the

temperature of the animal falls below normal. This regulation is to a high degree a cellular property and its insufficiency is also such. The general muscle weakness is also striking, which shows that the muscle cells are severely altered. It is of great interest in this connection that injections of cortical extracts are able to offset the extreme muscle weakness which occurs in adrenalectomized animals on the slightest bodily exertion. Likewise, the psychical apathy, and changes in the irritability and conductivity of the nerves, the rapid and extensive emaciation, the lowering of metabolism, the disturbances in digestion, defective excretion, the accumulation of poisons, the pigmentation of the skin, occurrence of abortion, etc., all of the pathology of adrenal insufficiency indicates the involvement of the entire organism. According to Alsterberg *adrenal insufficiency means a cellular insufficiency, in hypofunction of the adrenal cortex there occurs a general hypofunction and in adrenal hyperfunction a general cellular hyperfunction*. The adrenal cortex stands in close cellular relationship to every organ so that insufficiency of a single organ is followed by regulatory reactions in the adrenal cortex. Alsterberg further holds that the function of the adrenal medulla and of adrenalin is to act as regulators for the transport of the cortical lipoids. The same influences which act on the secretory activity of the cortex act also on the production of adrenalin by the medullary substance. In favor of this view are the anatomical relationships of the medulla to the sympathetic nervous

system and the intimate relationship of the medulla to the cortex. Alsterberg believes that it is possible that the cortical secretion consists of one or more phosphatids. In the Goldzieher hormone phosphoric acid was wanting. The adrenal secretion does not consist of cholesterol, in this regard the Aschoff school is right. But the secretion is without doubt to be regarded as a lipid, eventually it forms a combination of lipid and albumin, which agrees with the finding by Ciaccio in the cortical capillaries of a fuchsinophile substance. Off and on has the view been advanced that the adrenals regulate the presence of phosphatids in the body, eventually through a production of the same. Against this belief it has been urged that in adrenal insufficiency the phosphorus content of the body remains high, even rises in the blood. This does not exclude the possibility that phosphatids already produced and given over to the cells are

released and appear in the body fluids. Summing up Alsterberg's views, he believes that lipoids are given off into the cortical capillaries by the cells of the adrenal cortex. These lipoids are made use of by the lipophorous portions of the various organs and tissues. There exists a reciprocity between the secretory activity of the adrenal cortex and the functional activity of the body cells. On hypofunctional inactivity of the adrenal cortex there occurs a corresponding inactivity of the body cells, and in hyperfunction of the cortex a corresponding hyperactivity in the work and function of the body cells. In increased cell activity hyperactive reactions occur in the adrenal cortex, by lowered cell activity there occur hypoactive reactions in the cortex. It is probable that the chief function of the adrenal medulla is to serve as a regulator of the secretion and blood circulation through the cortical tissue.

## Abstracts

*The Progressive Anemia Following A Single Intra-Marrow Injection of B Welchii Toxins* By John C Torrey and Morton C Kahn (The American Journal of Pathology, March, 1929, p 117) This study is a continuation of the authors' investigations of the anemia produced in laboratory animals by a potent *B welchii* toxin. In a previous communication attention has been directed to the consistently and abnormally high *B welchii* counts in stools from pernicious anemia cases. These findings have been confirmed by Davidson, although Nye believes that the difference from the normal as regards the number of *B welchii* in the colon is more apparent than real. It was also shown that a transitory anemia with a blood picture strongly suggestive of the pernicious type in a number of features could be produced in monkeys by intravenous inoculations of such a toxin. Similar observations for rabbits have also been made subsequently by Patterson and Kast, and Barach and Draper, although these investigators consider the resulting anemia of a secondary rather than primary type. The anemia produced by actual infection of rabbits with whole cultures of *B welchii* was earlier studied by Cornell and Reed, Orr and Burleigh, and its pernicious-like features noted. It is the experience of the authors that the morphological and tinctorial blood changes in rabbits following the intravenous inoculation of toxin, while somewhat suggestive of pernicious anemia, are not so striking as in monkeys. The present research is concerned with the effects of the toxin on bone marrow, when introduced directly into the marrow and into the blood. It has been found that the *B welchii* is capable of producing two apparently distinct hemolysins, one of which is active both *in vitro* and *in vivo*, and the other, the more potent, causes

blood destruction *in vivo* but only to a slight degree, or not at all, *in vitro*. Comparative tests of the action of these two products on bone marrow have been carried out both when introduced directly into the marrow and into the blood. As a result of this work it was found that the single inoculation of 0.5cc of a potent sterile *B welchii* toxin into the tibial marrow of a rabbit or monkey gives rise to a chronic, persistent and finally often fatal anemia characterized by low hemoglobin content of the blood, low erythrocyte count and a color index generally above 1.0. Anisocytosis and at times poikilocytosis are pronounced. The single inoculation of 0.5cc of the toxin into the tibial marrow starts a degenerative process which apparently affects the whole marrow system. Definite evidence of beginning degenerative changes were noted in the marrows on the side of the body opposite the site of inoculation within eighteen hours. After twelve days the process was well advanced as shown by the marked mucous degeneration of the fat cells, great diminution in other normal marrow and blood forming cells and a marked increase in polymorphonuclear leukocytes. In rabbits which had died eleven or more weeks after the inoculation the marrows were found to be in an advanced stage of degeneration with fat cells replaced by a granular material and an extreme atrophy of the cellular elements. Nearly all the animals showed, at whatever stage examined, a rather more pronounced degeneration in marrows far removed than in that into which the toxin was injected. As intravenous inoculation of like or larger amounts of toxin causes no more than a transitory marrow injury the cause of the difference in effect is not clear. A single intravenous inoculation of *B welchii* toxin of the same dosage or a series of increasing doses gives rise to an anemia of the

same type as that resulting from marrow inoculation but is followed within three to four weeks by an immunity and a return of the blood to normal or nearly normal condition. Such intravenous inoculation of the toxin causes some mucous degeneration of the fat cells and an increase in the cellular elements of the marrow, particularly the leukocytes, but results in nothing like the destructive action of inoculation directly into the marrow. There is as yet no experimental data to explain the difference in effects of intravenous and intramarrow inoculation, but the suggestion may be made that the undiluted toxin in its destructive action on the bone marrow with which it is brought into direct contact may give rise to secondary toxic products particularly injurious to marrow tissue, and which on absorption throughout the blood and lymph are brought into contact with all the body marrows causing as grave an injury to those farthest removed as that into which the toxin was directly inoculated. It would seem probable that an experimental anemia produced in this way may prove helpful in the study of the treatment of pernicious anemia, particularly as regards the use of liver extracts and their standardization. It has been demonstrated by Beard, Clark and Moses that liver extract feeding to rabbits with the chronic anemia produced in this way is beneficial, resulting in a prompt and marked rise in reticulocytes, hemoglobin and red cell counts. There seems also to be a proportionality between the amount of liver extract given and the increase in number of red cells and hemoglobin content. The benefit, in fact, seems to parallel that occurring in a pernicious anemia patient on liver extract. Whipple has shown that a secondary anemia produced in dogs by repeated bleedings is only slightly benefited by feeding liver extract, although marked improvement follows the use of whole liver. It would seem, therefore, that the method of Torrey and Kahn offers a much more delicate method for potency titration. This form of experimental anemia, it is suggested, may prove a useful means for evaluating the potency of extracts of liver

and other organs as blood regenerating agents

*The Effect of Combined Feeding of Potassium Iodide and Anterior Lobe of the Pituitary Upon the Thyroid Gland* By Howard A. McCordock (The American Journal of Pathology, March, 1929, p. 171)

In a series of studies on compensatory hypertrophy of the thyroid gland Loeb has shown that the oral administration of potassium iodide in partially thyroidectomized animals not only fails to present hypertrophy but may even stimulate regenerative activity, while the feeding of anterior lobe of pituitary gland has an inhibiting effect, preventing even moderate degrees of hypertrophy and causes a hardening of the colloid and a lowering of the acinar cells. In view of this antagonistic action of these two substances on thyroid activity in compensatory hypertrophy, it seemed interesting to see if the stimulating effect of potassium iodide would counteract the inhibiting action of anterior pituitary substance, or vice versa. The experiments in this investigation concerned the effect of such combined feeding with potassium iodide and anterior pituitary on the thyroid gland, the result of administering each of these two substances separately to different animals and a comparison of these three types with normal thyroids from control guinea pigs. From these experiments it may be concluded that the marked mitotic proliferation induced so readily in the thyroid of guinea pigs by potassium iodide is prevented by anterior pituitary gland when both are fed to the same animal. These two substances administered separately are antithetical in their action on the thyroid, anterior pituitary gland depressing proliferative and probably also functional activity as indicated by a decided drop in the mitotic count below the normal level and by the appearance of small acini with a dense deeply staining colloid, while KI causes marked stimulation, in the initial stage of its action at least, with enormous increase in the number of mitoses and with the appearance of a softened, pale, vacuolar colloid containing phagocytic cells. The condition of the thyroid which follows feed-

ing of both these substances to the same animal is due to their direct action on the gland itself, and not an effect which they exert upon each other before absorption from the gastro-intestinal tract, because changes in the thyroid are the same whether both drugs are fed simultaneously or whether one is fed in the morning and the other in the evening precluding any chance of direct interaction between them. The stimulating influence of iodine and the depressing property of anterior pituitary substance can be balanced in such a manner that an approximately stationary or resting condition in the thyroid results. In some respects anterior pituitary substance produces changes in the thyroid gland analogous to those induced by thyroxin or thyroid itself. From these experiments it is impossible to determine the exact manner in which pituitary substance exerts its influence upon the thyroid gland. All that one can say is that in some way the oral administration of anterior pituitary tablets (Armour & Co) causes a depression in the activity of the thyroid with a marked lowering of the number of mitoses in the gland and with the production of medium-sized, or somewhat smaller, acini distended with hard colloid compressing the living epithelium into thin strands of cells. During the first stage of its action, potassium iodide, on the other hand, produces marked stimulation with enormous mitotic activity and a slightly softened colloid occasionally containing large numbers of phagocytic cells. The early proliferative change induced in the thyroid gland by potassium iodide is prevented by anterior pituitary when both these substances are fed to the same animal.

*Likeness and Contrasts in the Hemolytic Anemias of Childhood* By Thomas B. Cooley (Amer Jour of Diseases of Children, December, 1928, p 1257) There are three diseases of early childhood, apparently rather closely related not only in symptomatology, but probably also in fundamental etiology: congenital hemolytic icterus, sickle-cell anemia and the disease which has hitherto been included under the rather vague classification of von Jaksch's anemia,

or much better, as Cooley suggests under the more appropriate designation of erythroblastic anemia of childhood. In the present paper essential likenesses and differences between these three anemias are discussed. In all three conditions one must recognize either a congenital disease or a pronounced and peculiar congenital diathesis. Hemolytic jaundice and sickle-cell anemia are definitely hereditary and familial. The erythroblastic anemia is not known to be hereditary, obviously because its subjects are not known to reach adult life. Sickle-cell anemia is distinctly racial and possibly originally limited to a small section of the negro race. The erythroblastic anemia is so conspicuously more common in the Mediterranean races as to seem almost peculiar to them, while hemolytic jaundice, though more widespread than the other two, tends decidedly to be more frequent in certain regions and among certain people, and to appear only sporadically elsewhere. In other words, in all three the diathesis seems distinctly a matter of family or race. There are striking hematologic resemblance in the three diseases. Each seems to be characterized by a peculiar type of red cell. Microcytosis was recognized by Gäusslen and others as characteristic of hemolytic jaundice, and Gäusslen ascribed peculiar qualities to these microcytes. No other disease shows uniformly at its height so many erythroblasts as does erythroblastic anemia and after splenectomy their numbers are remarkable. Cooley regards them as a special form of cell. Hemolytic jaundice is said to show more reticulated red cells than any other disease. There is, however, but little difference in this respect between it and the other two sickle-cell anemia especially in the active stage showing extremely large numbers. Increased fragility of the erythrocytes to hypotonic salt solutions is generally recognized as a cardinal symptom of hemolytic jaundice. It is more common in this disease but occurs also in the other two. Urobilinuria, also, more common in hemolytic jaundice, may be present in either of the others. As to the white cells, hemolytic jaundice and sickle-cell anemia do not show any remark-



able characteristics. On the other hand erythroblastic anemia, the most serious and rapidly progressing, early shows evidence of pronounced bone-marrow irritation, which apparently is reflected in the production of increased numbers of leukocytes with the appearance in the blood of early forms. With the development of marked marrow hyperplasia the number of these cells may run to high figures. The extreme hyperplasia of the marrow characterizes erythroblastic anemia, it is less constant and less pronounced in sickle-cell anemia, and has not been especially noted in hemolytic jaundice. The behavior of the spleen in the three conditions shows both resemblances and differences. In all it must be assumed to have an active part in the hemolytic process, and it is probable that the histologic changes that take place in it are somehow the result of this activity. It is rather peculiar, then, that there should be such differences as may be noted in its size and structure. In hemolytic jaundice it is often little, if at all, enlarged, and is likely to vary in size with the amount of hemolysis going on, being particularly noticeable during the crisis. Histologically it shows a moderate fibrosis and an infiltration with erythrocytes. Sickle-cell anemia has similar crises and similar changes in the volume of the spleen. In this disease the spleen is early enlarged, but later shrinks to less than normal size, with the development of a peculiar fibrosis, amounting almost to cicatrization. When removed early its gross appearance is hardly distinguishable from that seen in hemolytic jaundice. In erythroblastic anemia the early enlargement is much greater than in the other two, and the increase is progressive, with less variation from time to time. The histologic changes here are rather more complex than in the other two. Removal of the spleen has different results in the three diseases. In hemolytic

jaundice, with the exception of rare cases of the pernicious type, the result is usually almost, if not quite, a complete cure. Without any remarkable immediate reaction, hemolysis stops or is greatly diminished, the anemia and the jaundice disappear and the patient is apparently well. In sickle-cell anemia after early splenectomy, there is also no pronounced immediate reaction. The patient seems somewhat improved, the anemia is less pronounced, but hemolysis is still observed, and the sickling is unchanged. In erythroblastic anemia splenectomy is followed by a remarkable increase of erythroblasts in the blood, lasting over years, and there seems to be little definite improvement in the patient. Hemolysis and jaundice, if present, may be temporarily lessened, but they return and the disease process continues as before. Cooley suggests that these three diseases might be thought of as three types of hemolytic jaundice, each dependent on a congenital diathesis, and each strikingly limited to familial or racial groups. Each is characterized by a peculiar, abnormal type of red cell, and much of the clinical symptomatology is due to hemolysis of these abnormal cells under the influence of the spleen and its associated tissues. Either physical or chemical abnormalities in all structures might be the reason for this increased susceptibility to hemolysis. As to the nature of these structural defects we possess no positive knowledge. A toxic theory could hardly have any application. Congenital abnormalities in the bone marrow is a plausible explanation and cannot at present be ruled out. Another possibility is that the failure of the bone marrow may result from an inadequate supply of proper material for blood-making, due to defective absorption or to some failure in the intermediate metabolism, whether or not due to a hormone deficiency.

## Reviews

*An Index of Differential Diagnosis of Main Symptoms* By Various Writers  
Edited by Herbert French, CBE (Military), MA, MD Oxon, FRCP, London Physician to H M Household, Physician and Lecturer, Guy's Hospital, Consulting Physician to Queen Alexandra's Military Hospital, Millbank Fourth Edition 1171 pages, 701 illustrations, 179 figures in color William Wood and Company, New York, 1928 Price in cloth, \$18 00

This work has been revised throughout, but its general principles remain the same as in the first edition. Over 30,000 copies of the previous editions have been sold, and the work has been translated both into Italian and Spanish. The book is a treatise on the application of differential diagnosis to all the main signs and symptoms of disease. It aims at being of practical utility to medical men whenever difficulty arises in deciding the precise cause of any particular symptom of which a patient may complain. It covers the whole ground of medicine, surgery, gynecology, ophthalmology, dermatology and neurology. It deals with diagnosis from a standpoint which is different from that of most textbooks, being an Index of Diagnosis, in that its articles on the various symptoms are arranged in alphabetical order, at the same time it is a work upon differential diagnosis in that it discusses the methods of distinguishing between the various diseases in which each individual symptom may be observed. Whilst the body of the book thus deals with symptoms, the general index at the end gathers these together under the headings of the various diseases in which they occur. Especial stress is laid upon the importance of using these two parts of the book together. The guiding principle throughout has been to suppose that a par-

ticular symptom attracts especial notice in a given case, and that the diagnosis has to be established by differentiating between the various diseases to which this symptom may be due. Treatment, pathology and prognosis are not dealt with except in so far as they may bear upon differential diagnosis. The book is unique in medical literature in principle and in its working out. The great demand for previous editions would indicate its utility to the medical profession, and it is hoped that the present edition will prove to be of as much service as its predecessors.

*Report of the International Conference on Cancer* London, 17-20th July, 1928  
Held under the auspices of the British Empire Cancer Campaign 588 pages  
William Wood and Company, New York, 1928 Price in cloth, \$12 00

This volume contains the addresses and abstracts of papers presented at the International Conference on Cancer held in London last July. These are grouped under the general heads: Etiology of Cancer, The Relative Values of Surgery and Radiation in the Treatment of Cancer, Methods of Treatment by Chemotherapy, Occupational Cancer, Early Recognition and Treatment of Cancer of the Stomach, Sarcoma of Bone, Cancer Cachexia, Cancer of the Lung, Diagnostic Methods in Relation to Cancer, Effects of Radium and X-Rays on the Blood, Vascular and Lymphatic Systems, with Special Reference to Malignant Growths, Biological Effects of Radium and X-Rays, Geographical and Racial Prevalence of Cancer, Public Action in Regard to Cancer. The work of this Conference is distinguished chiefly by its sterility of new ideas. Nothing new of importance was presented before it, and most of the papers consisted of a rehashing of old material. Nevertheless there is a cer-

tain value in this collection of material representing the collective cancer knowledge of the day, and this volume forms a convenient resumé of most of the lines of cancer thought and work of interest to present day workers. That it leads to nowhere is not so much the fault of the workers along these lines as it is the complexity and difficulty of the problem. Cancer investigation has again reached a blank wall against which it is bumping its head. The geneticists are squabbling over dominance and recessiveness, the adherents to the theory of specific infection are silenced, The Gye-Barnard bubble has been pricked, the colloidal lead treatment discredited and conservatism is asked for in the radium and x-ray treatment of cancer. Nevertheless, this volume contains much of great value, particularly with reference to occupational cancer. It is a well-printed volume.

*Methods and Uses of Hypnosis and Self-Hypnosis. A Treatise on the Powers of the Subconscious Mind.* By Bernard Hollander, M.D., M.R.C.S., L.R.C.P. 191 pages. The MacMillan Company, New York, 1928. Price in cloth, \$2.50.

This book is the result of thirty years' experience of experimental hypnosis and hypnotic treatment. Its main object is to draw attention to the importance of hypnosis and its phenomena in order to stimulate inquiry into what is still a mysterious and unexplored subject. Suggestion plays a very important part in our mental development, and in our intercourse with our fellows. No one can escape its influence. We are constantly receiving suggestions, or suggesting to others, though we are not always conscious of the power we are exercising. In hypnosis suggestibility is greatly increased. All hypnotic phenomena cannot be explained by suggestion, and certainly do not depend entirely on it, but can be produced without its influence. It is shown in this book that, contrary to common belief, sleep is quite unnecessary for the induction of hypnosis. In the author's opinion the wonderful phenomena produced in the hypnotic state depend on the bringing into prominence of what is termed the

subconscious mind, and utilizing it for practical ends. This state resembles that in which men of genius have achieved their highest creations, while completely oblivious of their physical sensations and external surroundings. In this state of passive concentration, when no impression from the external world reaches the brain, the mind can be directed to the bodily functions and extraordinary physiologic results obtained—results leading to spontaneous and lasting cures. Such hypnotic treatment is peculiarly successful in nervous and mental disorders and moral failings. To make the cures lasting it is absolutely essential to re-educate the patient—a task which, in the hypnotic state, is far easier to accomplish than in the waking state. Further, it is shown in this book that the study of hypnotic phenomena brings us nearer to an explanation of such mysterious manifestations as Thought Transference, Clairvoyance, Premonitions, etc. Hypnotism is no longer a matter for the showman, but for the physician and the psychologist. This book should help educated people to learn something of its facts. The author hopes that the records given will convince the reader that there are forces in human beings the presence of which, with our available knowledge, we can only surmise, and that the strange powers of hypnosis may unlock many doors and lead to the solution of many mysteries.

*Handbook of Physiology.* By W. D. Halliburton, M.D., LL.D., F.R.C.P., F.R.S., Emeritus Professor of Physiology, King's College, London, and R. J. S. McDowall, M.B., D.Sc., F.R.C.P. (Edin.), Dean of the Faculty of Medicine and Professor of Physiology, King's College, London. Eighteenth Edition. 902 pages. 500 illustrations, 3 colored plates. P. Blakiston's Son and Co., Philadelphia, 1929. Price in cloth, \$4.50.

Halliburton's Physiology has seen seventeen editions in twenty-nine years, a total of 116,000 copies. When in 1928 another revision became necessary, Professor Halliburton found that he needed help in preparing it, his successor Professor McDowall

was secured, and the latter's name has been added to the title of the book. There has been considerable rearrangement, both in the order of the chapters and within the chapters. Some have been rewritten, particularly many of the Nervous System, so as to bring Reflex Action up-to-date, and to admit of adequate treatment of Postural and Conditional Reflexes. The sections on the Autonomic Nervous System, the Control of the Circulation, the Carriage of Carbon Dioxide, the Maintenance of Body Neutrality, Vitamins, Ductless Glands, and Intermediate Metabolism are also for the most part new. Additions have been made on the following subjects: the Formation of the Blood and the Bile, Test Meals, Blood Groups, the Polygraph, recent work on the Spleen and Control of Respiration, the effect of Exercise on Respiratory Exchanges, and various other matters. To admit this new material anatomical detail has been reduced, but essential anatomy and physiologic histology have been retained. Many new diagrams have been added. Particular stress has been laid on the requirements of the medical student by omitting less essential details and emphasizing principles. The book has actually been reduced slightly in size. This edition of this classic textbook appears to be fully brought up-to-date. It retains the good qualities of the older editions in its clear and concise treatment of physiologic structure and function.

Mark's Hospital, New York City, Formerly Visiting Instructor, Schools of Nursing of Bellevue and Harlem Hospitals, New York City. 200 pages, 44 figures. The MacMillan Company, New York, 1928. Price in cloth, \$2.25.

It is difficult to select from a field so wide as that of Bacteriology the facts and principles with which the nurse must become familiar, since her work is not that of the bacteriologist or the technician. To her is delegated the important task of correlating the discoveries of the laboratory with the routine of the ward and the technique of the operating room. This textbook is offered in an attempt to simplify this work of selection and application, and an effort has been made to set forth the essential facts in a way in which they may be easily understood and to show how this knowledge may be used. The subject is treated in sixteen chapters comprising an Introduction, Plants Independent and Dependent, General Characteristics of Bacteria, Non-pathogenic Bacteria, Collecting of Pathological Specimens, How Bacteria are Studied, How Bacteria are Destroyed, Bacterial Activities in the Human Body, Bacteriology and Nursing Technique, Bacteriology in Surgery, Theories of Immunity, Application of Immunity Theories, Water and Milk, Important Pathogenic Cocci, Important Pathogenic Bacilli, and Other Important Pathogenic Organisms. These chapters set forth the essential facts in a way in which they can be easily understood, and show how this knowledge can be used. It is a satisfactory book for the purpose for which it is intended.

*Applied Bacteriology for Nurses* By Jean Martin White, R.N., Instructor in Sciences, School of Nursing of St

## College News Notes

Lieutenant-Colonel Edward G. Huber of the U S Army Medical Corps was elected President of the honorary public health society, Delta Omega, at its fifth annual meeting in Chicago last October, during the convention of the American Public Health Association

The Delta Omega Society now has about two hundred members belonging to six chapters at the Johns Hopkins School of Hygiene and Public Health, the Harvard University School of Public Health, the Massachusetts Institute of Technology, the University of Michigan, the Yale School of Medicine and the University of California

Dr Bernard Fantus (Fellow), Detroit, was elected Chairman of the advisory council of the League for the Prevention of Hay-Fever at a recent meeting

Dr Anton J Carlson (Fellow), Professor and Chairman of the Department of Physiology, University of Chicago, spoke before the Chicago Medical Society February 13 on "Attempts to Stimulate Physiologic Processes by Diathermy"

Dr Karl F Eschelmann (Fellow), Buffalo, and a staff of fourteen physicians will conduct a cancer clinic at the Buffalo City Hospital each Saturday morning. The clinic will have a small supply of radium at its disposal

Dr George Morris Piersol (Fellow), Philadelphia, addressed the Buffalo Academy of Medicine, section of medicine, February 13 on hemorrhage from the gastrointestinal tract

Dr Albert H Hoge (Fellow), Bluefield, West Virginia, addressed the Cabell Coun-

ty Medical Society recently on "Hypothyroidism"

Colonel Bailey K Ashford (Fellow), U S Army, retired, now Professor of Tropical Medicine and Mycology at the University of Porto Rico, represented the United States at the First International Conference on Tropical Medicine and Hygiene at Cairo, Egypt, in December

Dr E. B. Krumbhaar (Fellow), Philadelphia, is President of the Rush Society of the University of Pennsylvania

Dr Carl V Vischer (Fellow), Philadelphia, a member of the medical staff and Lecturer on Medical Nursing at St Luke's Hospital is Co-Author with Ruth D Smathers, B S, Dietician, and Mary A Moran, R N, of a small book on Diets. The book should serve as a valuable guide to physicians when ordering the commonly used diets

Dr Arthur C Morgan (Fellow), Philadelphia, has been appointed Chairman of the Disabled Soldiers and Medical Aid Committee of the Philadelphia County Council, American Legion. This appointment is one of the most important posts in the Council

Dr Charles D Aaron (Fellow), Detroit, Professor of Gastro-Enterology and Dietetics at the Detroit College of Medicine and Surgery, is author of a book, "Diseases of the Digestive Organs," published by Lea and Febiger, Philadelphia

Dr S Calvin Smith (Fellow), Philadelphia, delivered a lecture, "Hints on Heart Health," the first of a series of health and

economic talks at the Philadelphia County Medical Society on February 5

Dr Adolph H Nahman (Fellow), San Francisco, on February 1, 1929, was appointed Chief of the Medical Clinic and Associate Chief of the Medical Department of the Mount Zion Hospital, of San Francisco

Dr Paul F Whitaker (Fellow), Kingston, presented a paper on "The Treatment of Duodenal Ulcer" before the recent meeting of the Seaboard Medical Association at Washington, N C

Dr Whitaker was elected President of the Lenoir County Medical Society for the ensuing year at a meeting on February 10

Dr A R Foss (Fellow), Missoula, has been ill since August, 1928, with septic gallbladder and subdiaphragmatic abscess. He is convalescing now in Hollywood, Calif., and expects to resume his practice soon

Dr Samuel Ayres, Jr (Associate), Los Angeles, on January 23 addressed the Pacific Physiotherapy Association (Los Angeles) on treatment of skin diseases by light therapy

Dr Edwin G Bannick (Fellow), Rochester, Minnesota, spoke on "Nephritis" before the meeting of the Iowa and Illinois Central District Medical Association, January 17, at Davenport

Dr LeRoy Crummer (Fellow), Omaha, addressed the San Francisco County Medical Society, February 5, on "The Necessity of a Fad"

Dr William F Cheney (Fellow), San Francisco, was elected President of the Commonwealth Club of California for the ensuing year

Dr Emanuel Libman (Fellow), New York, donated a gift of \$10,000 to the Johns Hopkins University for the establishment of a lectureship in the history of

medicine, to be named the Hideyo Noguchi Lectureship

Dr Edwin L Gardner (Associate), Minneapolis, is Secretary of the Minneapolis Society of Internal Medicine. This Society recently announced its third annual prize of \$250 to be awarded "to the practicing physician, exclusive of members of this society, in the state of Minnesota who has been deemed most worthy to receive a prize in research in clinical medicine"

Dr Horace W Soper (Fellow), St Louis, recently addressed the Jackson County Medical Society (Kansas City) on constipation

Dr Edward E Cornwall (Fellow), Brooklyn, was one of the speakers at a symposium on pneumonia at the meeting of the Medical Association of the Greater City of New York, February 18

Among the speakers at the symposium held, February 26, by the Pittsburgh Academy of Medicine on the aims and accomplishments of organized medicine were the following members of the College: Dr Thomas G Simonton (Associate), President of the State Medical Society and William H Mayer (Fellow), former President of the Allegheny County Medical Society

Dr Arthur C Morgan (Fellow), Philadelphia, recently addressed the Harrisburg Academy of Medicine on cardiorenal disease

Dr Cyrus C Sturgis (Fellow), Ann Arbor, addressed the Montgomery County Medical Society, January 18, at Dayton on the modern treatment of anemia

The Chi Zeta Chi Medical Fraternity, founded at the University of Georgia School of Medicine in 1903, celebrated its twenty-fifth jubilee at St Louis, December 28-30. Having been exclusively located in southern medical schools, the fraternity decided to consider petitions from medical schools

in the north, east and west, and Dr Thomas Noxon Toomey (Fellow), St Louis, was elected supreme eminent master

At the annual meeting of the Radiological Society of North America in Chicago, December, 1928, Dr Maximilian J Hubeny (Fellow) was elected President

Dr Robert M Moore (Fellow), Indianapolis, on February 5 addressed the Summit County Medical Society at Akron, his subject being "Some Consideration in Heart Failure of the Anginal Type"

Dr McKim Marriott (Fellow), St Louis, and Dr Julius H Hess (Fellow), Chicago, were members on the faculty of the Graduate Course in Pediatrics for practitioners, which was given at the University Hospital in Oklahoma City, February 11-15, and arranged by the University of Oklahoma School of Medicine and the Extension Division

Dr Irving Gray (Fellow), Brooklyn, Associate Attending Physician at the Jewish Hospital, has been placed in charge of a newly created department of Gastro-Enterology at the same institution

Dr Hubert Work (Fellow), Colorado Springs, Secretary of the Interior during most of the administration of President Coolidge, resigned from the Cabinet in 1928 to become Chairman of the National Republican Committee. Dr Work formerly practiced medicine and was a member of the House of Delegates of the American Medical Association for many years. He was the first speaker of the House of Delegates and was President of the Association in 1921.

Dr William J Quigley (Associate), Lakewood, Ohio, has resigned as Assistant Clinical Professor of Medicine of the Rush Medical College

Surgeon General Hugh S Cumming (Fellow), Washington, D C, was one of the speakers at the fourth New York Health

Conference held at the Hotels Roosevelt and Biltmore, March 14-15, under the auspices of seven different state, local and national agencies

Dr Joseph C Doane (Fellow), Philadelphia, recently addressed the Lackawanna County Medical Society at Scranton on diseases of the right upper quadrant of the abdomen

Dr George R Minot (Fellow), Professor of Medicine, Harvard University Medical School, and Director of the Thorndike Memorial Laboratory, delivered, March 7-8, the second course of the William Sidney Thayer and Susan Read Thayer Lectureship in Clinical Medicine at Johns Hopkins University School of Medicine, Baltimore. Dr Minot's subjects were "Treatment of Pernicious Anemia" and "Treatment of Anemia Other Than Pernicious Anemia Particularly with Diet and Iron." This lectureship was endowed by a group of friends of Dr William S Thayer (Fellow) in 1927. Sir Humphrey Rolleston delivered the 1928 lectures.

Dr Ralph Kuhns (Associate), Chicago, was a speaker on the scientific program of the February 13 meeting of the Lake County Medical Society

Dr Edward J G Beardsley (Fellow), Philadelphia, addressed the Philadelphia County Medical Society, February 20, on the medical aspects of modern professional pharmacy

Dr William Engelbach (Fellow), St Louis, addressed the Los Angeles County Medical Association, March 7, on "Diagnosis and Treatment of Endocrine Diseases"

Dr Preston M Hickey (Fellow), Professor of Roentgenology, University of Michigan Medical School, was the guest of honor at the second Annual Meeting of the Indiana Roentgen Society, February 22. Dr Hickey's subject was "Lateral Teleroentgenography of the Chest"

Dr George R Minot (Fellow), Boston, resigned during March as head of the Medical Service of the Huntington Memorial Hospital for Cancer Research, and has been appointed successor of the late Dr Francis W Peabody at the Boston City Hospital

Dr Frank Smithies (Fellow), Chicago, recently addressed the Marquette-Alger County Medical Society on gastric hemorrhage

Dr George R Maxwell (Associate), Morgantown, addressed the Fayette County Medical Society, March 7, on "Early Diagnosis of Pulmonary Tuberculosis"

Dr Robert A Peets (Fellow), Colfax, addressed the Pasteur Society of Central California (San Francisco), February 27

Dr William A White (Fellow), Washington, D C, was guest of honor at a dinner at the University Club (Baltimore), March 15 Dr White's subject was "The Psychiatrist Looks at Crime"

Dr Harold W Jones (Fellow), Philadelphia, on March 8, addressed the Lycoming County Medical Society (Williamsport) on "Blood Transfusions and Blood Dyscrasias"

Dr William F Lorenz (Fellow), Madison, has been appointed Colonel of the 135th Medical Regiment of the Wisconsin National Guard

Dr Maurice C Pincoffs (Fellow), Baltimore, addressed the Baltimore City Medical Society, March 15, on "Paroxysmal Hypertension Due to Adrenal Tumor"

Bernard L Wyatt (Fellow), Tucson, resigned on April first as Director of the Desert Sanatorium and as President of the Board of Directors Dr Allen K Krause (Fellow), Baltimore, has succeeded Dr Wyatt as President of the Board of Directors

Dr Turner Z Cason (Fellow), Jacksonville, spoke before the quarterly meeting of the Leon-Gadsden-Liberty-Wakulla-Jefferson County Medical Society, Tallahassee, on "Cardiac Disease in the Syphilitic"

Dr Elliott P Joslin (Fellow), Clinical Professor of Medicine, Harvard University Medical School, addressed the Wayne County Medical Society, March 19, on "Present Thoughts on Diabetes and Their Application to Treatment"

Dr Charles H Neilson (Fellow), St Louis, spoke before the Waterloo Medical Society, January 16, on the nervous patient

Dr Anthony Bassler (Fellow), New York, addressed the New York Gastro-Enterological Association, April 1, on "The Colopathies" Doctors Walter A Bastedo (Fellow), New York, Charles Eastmond (Fellow), Brooklyn, Dr Max Einhorn (Fellow), New York, and Albert F R Andresen (Fellow), Brooklyn were discussants

One of the floors of the new Maternity Department of the Georgetown University Hospital, Washington, will bear the name of Dr George M Kober (Fellow), who recently retired as Dean of the Georgetown University Medical School after many years' service

Dr Andrew C Ivy (Fellow), Chicago is Secretary of a Committee which met March 18 at the City Club of Chicago to formulate plans to oppose the antivivisection bill which was introduced, March 7, in the Illinois legislature

Dr John A Lichty (Fellow), Clifton Springs, addressed the Pinellas County Medical Society, March 8, on "Achyria Gastrica and its Significance in Relation to other Diseases," with lantern slides

Dr Lawrence Itchfield (Fellow), Pittsburgh, is a member of the Publication Committee of the Pennsylvania Medical Journal Dr George E Holtzapple (Fellow),



York, Dr H Brooker Mills (Fellow), Philadelphia, and Dr. Arthur C Morgan (Fellow), Philadelphia, are Associate Editors of this Journal.

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Dr Richard Hayes (Fellow), D M R E (Camb) of Longview, Wash, addressed the Annual Convention of the Radiological Society at Chicago, December 7, 1928, on Chronic Duodenal Ileus

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Dr C V Weller of the department of pathology of the University of Michigan presented a paper on "Degrees of Entdiferentiation in Primary Carcinoma of the Lung," at the Chicago Meeting of The American Association for Cancer Research March 27 At the meeting of the American Association of Pathologists and Bacteriologists, on Friday, March 29, he read a paper on "Calcification of the Kidneys in Bismuth Poisoning"

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Dr Aldred Scott Warthin presided at the Chicago meeting of the American Association for Cancer Research, March 27th in place of Dr J F Schamberg who prevented by illness from attending Dr Warthin presented papers before this association and also before the American Association of Pathologists and Bacteriologists on March 28.

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#### MEETING AND DINNER BY MILWAUKEE MEMBERS

The following Milwaukee members of the American College of Physicians held a meeting and were entertained at dinner at the home of Dr Rock Sleyster, Wauwatosa, Wisconsin, on February 11 Dr Arthur J Patek, Dr Louis M Warfield, Dr J Gurney Taylor, Dr R W Blumenthal, Dr Oscar Lotz, Dr Alfred W Gray, Dr C H Stoddard, all of Milwaukee, Wisconsin

Dr Sleyster is the member of the Board of Governors representing Wisconsin, and, therefore, sponsored the meeting College matters in general were discussed, plans for attending the Boston Clinical Session were made and a survey of eligible candidates

for Fellowship and Associateship was considered Discussion was entered into concerning whether Dermatology and Roentgenology are properly classified as branches of Internal Medicine, and whether men practicing these specialties should be eligible for membership in the American College of Physicians (*Editor's Note* Both Dermatologists and Roentgenologists are at present eligible for membership, and in fact a considerable number are represented in the membership) It was further the consensus of opinion of this group that the annual meeting would be more valuable if papers were open for discussion and someone prepared to open the same Furthermore, the suggestion was advanced that the member of the Board of Governors for any state should be elected by the Fellows and Masters from that State, instead of by the present plan of election of all Governors at the General Business Meeting of the College

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"Dr J W Torbett, Marlin, Texas, recently delivered an address before the Central Texas District Medical Society in Temple, Texas, on the subject of "Systemic Diseases from Focal Infections of Peribronchial and Other Lymphoid Glands Following Influenza" A similar address will be delivered before the State Medical Association at Brownsville in May Dr Torbett was recently elected Vice-President of the American College of Physiotherapy at its meeting in Chicago and has been appointed toastmaster of the annual banquet and Chairman of the Section of Dietetics of the American Electrotherapeutic Association which meets in Indianapolis this coming September

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Dr Anthony Bassler (Fellow) read a paper on the "Biological Importance of the Intestinal Tract" before the West End Medical Society on March 1 And will present "Some Treatment Points on Gastroduodenal Ulcer" before the North Bronx Medical Society on March 19, "The Colopathies" before the New York Gastroenterological Association April 1, And "The Significance of Biological Intestinal States

in the Specialism" before the Progressive Medical Society April 2. So far this Winter Dr Bassler has presented 9 contributions on intestinal biological subjects, has addressed 27 medical organizations on gastroenterological subjects, and read papers in 11 states

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### OBITUARY

Dr Charles Lyman Greene (Fellow), Saint Paul, died January 19, 1929, of cerebral hemorrhage, aged 66 years

Dr Greene was born in the town of Gray, Maine, the son of a surgeon. He began the study of medicine at the University of Michigan, but later changed to the University of Minnesota College of Medicine, from which he graduated in 1890. After pursuing postgraduate study in Vienna, he was appointed first assistant city physician of Saint Paul. Later he took postgraduate work at Harvard and Johns Hopkins Universities, and became Lecturer in Applied Anatomy at the University of Minnesota, 1892-94, Professor of same 1894-97, Professor of Clinical Medicine and Physical Diagnosis same 1897-1903, Professor of Therapy and Practice same 1903-09, Professor of Medicine and Chief of the Department of Medicine and Chief of the Clinic at the University of Minnesota Hospitals, 1909-15. Dr Greene was Chief of Staff of St Luke's Hospital from 1925 to the time of his death, and had also been acting as Consulting Physician to the State Hospital for Crippled Children and Attending Physician to the Miller Hospital. During the World War, he was commissioned Lieutenant Colonel in the Medical Corps of the U S Army,

and at the time of his death held the rank of Colonel in the Medical Reserve

He was a member of his County Medical Society, ex-President of the Minnesota State Medical Association, a Fellow of the American Medical Association, a member of the American Therapeutic Society, a member of the Association of American Physicians, and a Fellow of the American College of Physicians since December 29, 1916. He was formerly Medical Director of the Minnesota Mutual Life Insurance Company and President of the National Association of Life Insurance Examiners

Dr Greene was well known nationally as a medical author. His articles appeared frequently in local medical journals and were published in many national journals. He was the author of a book on Medical Examination for Life Insurance, but his most important work was his Medical Diagnosis, which was published through six editions, the last appearing in 1926

Dr Greene's generosity and equanimity endeared him to a host of friends both within and outside the ranks of the profession

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Dr John Craig Taylor (Fellow), Chelsea, Oklahoma, died March 4, 1929, aged 55

Dr. Taylor was born at Columbus, Kentucky, attended the University of Louisville and received his Medical Degree from that institution in 1898. He pursued postgraduate study at the Harvard Medical School, the Chicago Polyclinic and the Tulane University,

of Louisiana. He also was a frequent visitor to the Mayo Clinic at Rochester, Minnesota, and as late as 1926, pursued organized extension courses offered by the University of Oklahoma. He was a member of the Rogers County Medical Society, the Oklahoma State Medical Association, the American Medical Association, the Medical Association of the Southwest and a Fellow of the American College of Physicians since March 4, 1928, having been elected during the Twelfth Annual Clinical Session at New Orleans.

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JOHN PHILLIPS, M.D.

The tragic death of Dr. Phillips, by gas poisoning in the Cleveland Clinic Disaster, closed one of the most brilliant careers in Cleveland Medicine. In twenty-three years he rose from resident physician at Lakeside Hospital to Assistant Professor of Medicine in Western Reserve Medical School, visiting physician to Lakeside Hospital, consulting physician to Rainbow, St. Johns and Maternity Hospitals and finally to director and chief of the Medical Division of the Cleveland Clinic. In addition, through his early association with Dr. Edward Cushing, he acquired a large private practice and retained the confidence of many of the old Cleveland families. Later as medical chief at the Clinic, he carried on an enormous consulting practice.

Dr. Phillips was greatly interested in the American College of Physicians from its beginning, and was elected to the Board of Regents in 1923. He has been very active in the affairs of the College since that time, serving on the Executive Committee, on the Com-

mittee on Constitution and By-Laws, and as chairman of the Committee on Postgraduate Medical Instruction. He was the local Chairman of Arrangements for the Annual Session in Cleveland in 1927.

Dr. Phillips was born in Welland, Ontario, in 1879, and had his early training in the public schools and at the Model Teachers Training School of Welland. He received his M.B. degree from the University of Toronto in 1903. Following this he served as interne and resident physician at Lakeside Hospital, Cleveland, until 1906. During this period his ability, extraordinary industry, working capacity, and hard practical common sense attracted the attention of Dr. Cushing, then visiting physician at Lakeside, and led to the association which formed the basis of his career. He also did postgraduate work at Johns Hopkins Hospital. In his early years of practice he paid especial attention to pediatrics, and became attending physician to the Babies Dispensary and Hospital. He never lost his interest in this field. He later became an active member of the American Child Hygiene Association, also of the American Heart Association, the Association for Study of Internal Secretions, the American Gastro-enterological Association and other national organizations.

The most outstanding characteristics of Dr. Phillips' personality were simplicity, directness, poise and a remarkable sense of relative values. He drew conclusions rapidly and used his own experience very effectively in the direction of progressive growth. Although possessed of a high degree of mental acumen and a remarkable memory he

regarded long, continuous, hard work as the main road to success. Work was his philosophy of life, he practically never played. Medical activities of some kind seemed to satisfy all his recreational needs. He was always optimistic, constructive and helpful. Although never fond of writing, he so disciplined himself in all necessary phases of medical life that he published over fifty articles in various journals, a section on "Diseases of the Pleura" in "Cecil's Medical System" and just before his death delivered his manuscript on "Diseases of the Gall Bladder and Liver" for a series of monographs to be published in book form by Dr. Henry Christian.

Although never attracted to military life, Dr. Phillips accepted the call of service in 1918 and became captain in the Medical Corps of the Army at Camp Jackson in South Carolina and consultant in charge of the cardiovascular board at Camp Upton. Upon returning to civil life, the advantages of group practice as observed in the army appealed to Dr. Phillips, and when the opportunity of becoming a co-developer of the Cleveland Clinic with Drs. Crile, Lower and Bunts came to him, he was thrilled with the idea of a new objective for which to work. His energy, loyalty, and ability contributed consistently to the growth of the institution. He had entire charge of the medical division.

The untimely death of Dr. Phillips is a great loss to the Cleveland profession, and to the official family of the American College of Physicians.

(Contributed by V. C. Rowland, M.D., Cleveland, Ohio)

## SHOULD THE COLLEGE CONDUCT A PLACEMENT SERVICE?

From time to time, suggestions have been received that the College should organize a Placement Service, whose object it would be to assist its members in locating able assistants, laboratory workers, technicians, etc., and also to assist members who seek new locations or connections. This would necessitate the setting up of records in the Executive Offices of lists of vacancies and lists of available candidates. The College could not, it is thought, assume any responsibility in respect to the success of candidates or the satisfaction of appointments, but it could perform that service of getting those who are seeking appointments in touch with those who have vacancies.

During recent months, the Executive Secretary has been asked to locate candidates for a number of positions, such as the following: (a) Laboratory worker with medical degree to take full charge of a laboratory in Panama City, (b) Assistant Physician to an Internist in Boise, Idaho, (c) Associate Secretary of the Public Health Federation of a city in Ohio, (d) House Surgeon for a large industrial firm near Philadelphia. Salaries in these positions varied from \$3,500 to \$6,000.

Members of the American College of Physicians who read this article are requested to express their opinions by letter to Mr. E. R. Loveland, Executive Secretary, 133-135 S. 36th Street, Philadelphia, Pa.

# INDEX

<b>A</b> BORTION, Septic, Endocarditis		1054
Following	912	
Abstracts	113, 228, 298, 384,	422
487, 576, 692, 832, 973, 1113, 1229, 1349		
Abuse of Digitalis	261	
Acid Mouth, Treatment of	550	
Acoin in Therapy of Diabetes	693	
Activation of Insulin in Non-Diabetics	976	
Acute Rheumatic Fever	108	
Adams, R B	1162	
Adamson, G L	487	
Address, Convocation	127	
Adrenal Cortex, Function of	1346	
Adrenalin in Malaria	1343	
Agramonte, A	138	
Agranulocytic Angina	542	
Agular, R	1341, 1343	
Albuminuria and Nephritis Following		
Toxin-Antitoxin	667	
Albuminuria, Postural	1047	
Allan, W	542	
Allen, F. M	203	
Anderson, J P	248	
Anemia Following Single Injection of		
B welchii Toxin	1349	
Anemia, in Myxedema	215	
Anemias, Hemolytic of Childhood	1351	
Anemias, Human, Effect of Nuclear		
Extractives	603	
Aneurysm, Dissecting of Aorta	658	
Angina, Agranulocytic	542	
Angina, Pectoris	115, 401	
Angina, Tobacco	577	
Anomaly, Cardiovascular	948	
Anoxemia of Myocardium	115	
Aorta, Symptoms of Dissecting An-		
eurysm of	658	
Aortic Insufficiency	113	
Aortic Ring, Congenital Atresia of	422	
Aortic Valve, Rupture of	113	
Appendiceal Amebiasis, Histopathology		
of	948	
Appendicitis, Chronic, from Viewpoint		
of Internist	1081	
Aristotle, Our Debt to	1261	
Arnett, J. H	231	
Arteries, Coronary, Sclerosis of	1253	
Ash of Liver in Pernicious Anemia	230	
Atelectasis, Massive		1054
Atresia, Congenital, of Aortic Ring		422
<b>B</b> ACKACHE, Etiology of		807
Barsky, J		401
Bartlett, W M		334
Basal Metabolism in Polycythemia		
Vera		1155
Base, Total, in Gastric Contents		1185
Bassler, A		192
Bath, Reaction to Cold		384
Bauer, J		127
Bence-Jones Protein in Pleural Effu-		
sion		881
Berghoff, R S		59
Berglund, H		471
Berman, P		298
Bernstein, M		682
Bettman, H W		509
Biochemical Approach to Study of		
Personality		576
Birkhaug, K E		524
Bishop, L F		352
Black Tongue and Pellagra		388
Blackwater Fever		316
Bliss, T L		1155
Block, E B		531
Bloedorn, W A		261
Blood Changes in Syphilis		578
Blood, Differential Count in Active		
Pulmonary Tuberculosis		622
Blood Dyscrasias Following Neoars-		
phenamine		488
Blood, Effect of Exclusive Meat Diet		
on		975
Blood Sugar and Blood Pressure		1230
Blood Uric Acid		367
Boston as a Medical Center		861
Bowcock, H M		832, 923
Bowel, Management of Common Dis-		
eases of Lower		1323
Brain Disease, Organic, Relation to		
Epilepsy		531
Bridges, M A		367
Broad Tape-Worm		693
Brockbank, T W		503
Brooke, R		281
Brooke, H		83

- Bronfin, I D 833  
 Brown, P W 177  
 Brown, W L 230  
 Bumstead, J H 1229
- CAJORI, F A** 1243  
 Calcification of Heart Muscle, Focal 936  
 Cameron, A F 487  
 Cameron, O J 1265  
 Cancer, Hunter's Views on 222  
 Cancer of Internal Organs 650  
 Carbohydrate Tolerance and Insulin 1001  
 Carcinoma of Lungs, Clinical Signs and Symptoms 725  
 Carcinoma of Stomach, Operability and Hemoglobin Percentage 503  
 Cardiac Lesions Coincident with Pulmonary Tuberculosis 833  
 Cardiology, The Practice of 352  
 Cardiovascular Anomaly 948  
 Cardiovascular Findings in Syphilitic Women 231  
 Cardiovascular Lesions Following Chest Injuries 1013  
 Cason, T Z 309  
 Castellani, A 155  
 Changes in Livers of Copper-fed Animals 835  
 Chesney, A M 385  
 Chester, J L 1175  
 Child, The Preventorium 833  
 Christian's Syndrome 1277  
 Christie, R V 832  
 Cirrhosis of Liver and Syphilis 932  
 Clinical Manifestations in Tuberculosis 1  
 Clinical Tuberculosis 1  
 Close, K M 1185  
 Cocke, C H 1054  
 Cohen, P 578  
 College News Notes 121, 236, 306, 395, 494, 584, 698, 841, 984, 1121, 1237, 1356  
 Coma Diabeticum, Kidney Changes in 693  
 Common Sense and Life Extension 571  
 Communicable Diseases, Effect on Thyroid 1113  
 Composition of Human Sweat 1243  
 Congenital Atresia of Aortic Ring 422  
 Congenital Heart Lesions 1115  
 Constitutional Entity of Exophthalmic Goiter and Toxic Adenoma 533  
 Cooke, J V 518
- Cooley, T B 685, 1351  
 Coronary Arteries, Sclerosis of 1253  
 Coronary Thrombosis 248  
 Costa-Mandry, O 1198  
 Crouter, C Y 1243
- DANZER, C S** 239  
 Dental Education of the Physician 435  
 Diabetes and Glycosuria 1328  
 Diabetes Mellitus, Etiology of 1209  
 Diabetes Mellitus in Negroes 832  
 Diabetes Mellitus, Treatment of 334  
 Diabetes Mellitus, Treatment with Acorn 693  
 Diabetes Mellitus, Treatment with Diet 645  
 Diabetic Therapy 269  
 Diabetic Treatment 203  
 Diagnosis of the Anemias 463  
 Diathermy, Experimental Study of 832  
 Dieckmann, W J 834  
 Dietetic Management of the Diabetic 325  
 Difficulties in the Diagnosis of Cancer 650  
 Digitalis, Abuse of 261  
 Disorders, Chronic Pancreatic 192  
 Dochez, A R 673  
 Downs, W G 810  
 Drake, J R 822  
 Duke, W W 463  
 Dyspnea, Pathogenesis and Treatment of 239
- ECLAMPSIA, Hepatic Lesions in** 834  
 Editorials 108, 222, 294, 373, 482, 571, 689, 827, 968, 1108, 1223, 1346  
 Education, Dental, of the Physician 435  
 Eggers, H E 386  
 Elden, C A 230  
 Electrocardiographic Studies of Transposition of Viscera 963  
 Elmer, A W 1114  
 Emetin, Its Effect on Rabbit's Heart 298  
 Encephalitis, Etiology and Treatment 1070  
 Endamiasis, Treatment of 177  
 Endocarditis Following Septic Abortion 912  
 Endocarditis of Pulmonary Cusps 665  
 Endocrine Dystrophies and Mental Subnormalities 810  
 Endocrine Factor in Rheumatism 33  
 Epidemiology of Undulant Fever in Iowa 453

- Epilepsy, Extracerebral Causes of 104  
 Epilepsy, Relation of Diet and Endocrine Disturbances to 678  
 Epilepsy, Relation of Organic Brain Disease to 531  
 Epilepsy, Treatment by Ketogenic Diet 1300  
 Erysipelas, Etiology of 524  
 Erythrocytes, Familial Occurrence of Elliptical 1162  
 Etiology of Backache 807  
 Etiology of Diabetes Mellitus 1209  
 Etiology of Encephalitis 1076  
 Etiology of Erysipelas 524  
 Etiology of Rheumatic Fever 637  
 Etiology of Tropical Sprue in Porto Rico 1198  
 Exophthalmic Goiter, Constitutional Entity of 553  
 Experimental Study of Diathermy 832
- F**ACTORS in Pathogenesis of Tuberculosis 21  
 Familial Occurrence of Elliptical Erythrocytes 1162  
 Familial Occurrence of Glycosuria 923  
 Farbar, M E 875  
 Feemster, R F 289  
 Feliciano, T R 298  
 Fever, Blackwater 316  
 Fever, Research in Yellow 138  
 Finsterer, H 385  
 Flatulence, Causes of 456  
 Flooded Area, Public Health in 297  
 Flinn, F B 835  
 Flinn, J W 622  
 Fortune, C H 912  
 Francois, A 1114  
 Friedbacher, K F 230  
 Frobisher, M 1229
- G**AGER, L T 658  
 Galambos, A 1328  
 Gastric Contents, Total Base in 1185  
 Gastric Tuberculosis 1265  
 Gastritis Phlegmonosa 385  
 Germ-plasm, Human Mixtures 373  
 Geyelin, H R 678  
 Glioma of Centrum Semiovale 815  
 Glomerular Lesions Produced by Streptococcus Viridans 1229  
 Glycosuria and Diabetes 1328  
 Glycosuria, Familial 923
- Goeckerman, W H 428  
 Golf, Physiological Effects of 827  
 Gordon, H 1309  
 Gordonier, H G 815  
 Graves' Disease, Preoperative Treatment of 487
- H**ALL, W E 545  
 Halley, C R 385  
 Hardy, A V 488  
 Hartman, H R 503  
 Hawaii, Medical Observations in 373, 482  
 Heart Block, Complete, Autopsy Finding in 669  
 Heart Disease, Syphilitic 973  
 Heart Muscle, Focal Calcification of 936  
 Heat Stroke 1113  
 Heilmann-Frosien, A 299  
 Hematologic Study of Elliptical Erythrocytes 1162  
 Hemoglobin Percentage in Carcinoma of Stomach 503  
 Hemolytic Anemias of Childhood 1351  
 Hemopoietic Effect of Nuclear Extractives 603  
 Hemorrhagic Glomerular Lesions 1229  
 Hepatic Lesion in Eclampsia 834  
 Herold, A A 269  
 Hirsch-Kauffmann, H 299  
 Histopathology of Appendiceal Amebiasis 1081  
 Hogenauer, F 692  
 Hogler, F 974  
 Howard, C P 113  
 Hunter's Views on Cancer 222  
 Hunter, W C 1162  
 Hypertonia, Arterial 1230  
 Hypothyroidism 446
- I**NDIVIDUALIZATION in Internal Medicine 127  
 Infection with Entameba Histolytica 171  
 Iodized Oil in Respiratory Tract of Dog 230  
 Insulin, Action on Lipochromemia and Xanthosis Diabetica 1114  
 Insulin, Activation of, in Non-diabetics 976  
 Insulin Activity, Inhibition of 578  
 Insulin and Carbohydrate Tolerance 1001  
 Insulin Treatment, Hyperthyroidism During 971  
 Intestinal Amebiasis 171

- Intestinal Tuberculosis 59
- JAMES, W M**
- Joforth, J L 171
- Jones, N W 275
- Joslin, E P 603
- KAHN, M C** 1001
- Kahn, M H 1349
- Kahn, S 401, 1013
- Karelitz, S 1013
- Keefer, C S 578
- Kennedy, W R 115
- Ketogenic Dietary in Migraine 488
- Ketogenic Diet in Treatment of Epilepsy 341
- Kidney Changes in Insulin Treated Coma 1300
- Kimbrough, R D 693
- King V DeP 973
- Kisch, F 936
- Klopstock, F 1230
- Krantz, J C 578
- Kraus, E J 1209
- Krause, A K 693
- Krysolgan in the Treatment of Lupus 21
- LANDRON, F** 428
- Larsell, O 1198
- Leader, S D 603
- Leake, W H 578
- LeDuc, D M 298
- Legal Medicine, Malaria in 932
- Leprosy, Early Manifestations of 1341
- Lesions, Cardiovascular, Following Chest Injury 482
- Leukemia in Mice, Experimental Transmission 1013
- Lewis, D S 1230
- Lieb, C W 66
- Life Extension and Common Sense 975
- Life Insurance and Syphilis 571
- Lipochromemia, Action of Insulin on 1236, 1237
- Lipoid Cell Hyperplasia 968
- Liver Diet and Tar Cancer 1114
- Liver Diet in Pernicious Anemia 1114
- Livers of Copper-fed Animals 471
- Lower Bowel, Management of Common Diseases of 825
- Lungs, Primary Carcinoma of 1323
- Lupus Erythematosus, Krysolgan in Treatment of 725
- Lymphadenopathies, Blood as Diagnostic Aid 428
- Lymphosarcoma, Type of Thymoma 747
- Lyttle, J D 1063
- MacDOWELL, E C** 747
- MacLean, D L 1230
- Maisin, J 1253
- Malaria, Adrenalin in 1114
- Malaria in Legal Medicine 1343
- Malpighi, M 1341
- Marcovici, E E 1108
- Massive Atelectasis 881
- Matthews, F P 1054
- McCann, W S 875
- McCordock, H A 230
- McKinley, E 1350
- McLester, J S 230
- McSweeney, C J 348
- Measles, Specific Prophylactic Measures in 229
- Measurements of Renal Veins 518
- Meat Diet, Effect of Exclusive 1047
- Medical Observations in Hawaii 975
- Medical Research in the South 373, 482
- Medication, Parathyroid and Thyroid 309
- Merbaphen, Use of 66
- Mercer, C D 97
- Mercuric Chloride, Acquired Resistance to 667
- Metadysentery 796
- Meulengracht, E 155
- Migraine, Ketogenic Dietary in 975
- Miller, R 341
- Moorman, L J 228
- Morbus Bascdowii and Pernicious Anemia 1216
- Morbus Caeruleus 975
- Mortality Rate in Cancer, Increased 1223
- Murdock, F P 386
- Musser, J H 545
- Myeloma, Multiple 1236, 1237
- Myocardium, Anoxemia of 881
- Myxedema, Anemia in 115
- NEGROES, Diabetes Mellitus in** 215
- Nicoarsphenamine, Blood Dyscrasias Following 832
- Neoplasia, Resistance to 48
- Nephrosis, Chron c 272



- Newburg, L H 645  
 Nicholson, D. 113  
 Nokes, H. T 603  
 Nuclear Extract in Anemias 603
- O**BSERVATIONS on Intestinal Amebiasis 171  
 Olesen, R 1113  
 Olmsted, W H 325  
 Operability and Hemoglobin Percentage in Carcinoma of Stomach 503  
 Oppenheimer, B S 577
- P**ANCREATIC Disorders, Chronic 192  
 Parathyroid Medication 66  
 Parotid and Pancreas, Possible Relationships 294  
 Parsonnet, A E 963  
 Pathogenesis of Dyspnea 239  
 Pathogenesis of Gastrogenous Tetany 300  
 Pathogenesis of Tuberculosis 21  
 Pellagra and Black Tongue 388  
 Pemberton, R 1243  
 Peripheral Circulation in Tobacco Angina 576  
 Pernicious Anemia and Morbus Basedowii 975  
 Pernicious Anemia, Effect of Ash of Liver 230  
 Pernicious Anemia, Liver Diet in 471  
 Personality, Biochemical Approach to 576  
 Phillips, B I 603  
 Philpott, N 422, 948  
 Physiological Effects of Golf 827  
 Pituitary and Potassium Iodide Feeding 1350  
 Pleural Effusion, Bence-Jones Protein in 881  
 Pneumonia, Treatment with Potassium Permanganate 1175  
 Polycythemia Vera, Basal Metabolism in 1155  
 Postinfluenzal Vomiting 1194  
 Postural Albuminuria 1047  
 Potassium Permanganate in Pneumonia 1175  
 Pottenger, F M 1  
 Practice of Cardiology 352  
 Precordial Stress 367  
 Profession, Our Changing 685  
 Pseudosyphilis, Problem of 1139  
 Pulmonary Tuberculosis 56
- Pulmonary Tuberculosis, Cardiac Lesions in 833  
 Pulmonary Tuberculosis, Differential Blood Counts in 622  
 Pulmonic Cusps, Ulcerative Endocarditis of 665  
 Purpura, Thrombopenic, in Agranulocytic Angina 542  
 Purpuric Skin Manifestations 97
- Q**UINAN, C 1047
- R**ABBIT'S Renal Epithelium and Mercuric Chloride 796  
 Ralli, E P 577  
 Ray, H M 941  
 Redisch, W 1115  
 Renal Veins, Measurements of 1047  
 Research in Yellow Fever 138  
 Resistance to Mercuric Chloride 796  
 Resistance to Neoplasia 275  
 Reswick, W H 115  
 Response of Chronic Nephrosis 66  
 Reticular-Endothelial System, Lipoidosis of 1277  
 Reviews 117, 232, 302, 390, 491, 580, 695, 836, 978, 1116, 1232, 1353  
 Rheumatic Fever, Acute 108  
 Rheumatic Fever, Clinical Manifestations of 637  
 Rheumatism, Acute in Childhood 229  
 Rheumatism in Children, Dietetic Aspects of 229  
 Rheumatism in Children, Influence of Environment 228  
 Rheumatism, Treatment of 83  
 Rich, A R 1229  
 Rich, G J 576  
 Richards, G G 771  
 Richter, M N 1230  
 Rickets, Influence of Tropics on 281  
 Riley, W H 384  
 Ringworm of Hands and Feet 386  
 Rosenberg, L 747  
 Rosler, H 1115  
 Rowland, R S 1277  
 Rowntree, L G 97  
 Rupture of Aortic Valve 113  
 Rush, J E 550
- S**ALICYLATE Therapy 367  
 Salzman, S R 1076

- Sanders, L C  
 Scarlet Fever  
 Scheps, M  
 Schnabel, T G  
 Schnack, A G  
 Schönbauer, L  
 Scleroderma, Diffuse  
 Sclerosis of Coronary Arteries  
 Scliver, W deM  
 Selye, H  
 Simon, Saling  
 Simpson, V E  
 Skin Manifestations, Purpuric  
 Small, J C  
 Smith, D C  
 Smith, E E  
 Smith, W A  
 Snell, A M  
 Spirit, The Scientific  
 Sprue, Tropical, Etiology of  
 Standard for Beri-beri Preventing  
   Rices  
 Status Lymphaticus  
 Steinitz, H  
 Stokes, J H  
 Stone, C F  
 Stone, W J  
 Streptococcus Viridans, Glomerular  
   Lesions  
 Sullivan, W E  
 Swan, J M  
 Sweat, Human, Composition of  
 Symptoms of Dissecting Aneurysm  
 Syndrome, Christian's  
 Synthalin, Toxic Action of  
 Syphilitic Blood Changes  
 Syphilitic Heart Disease  
 Syphilis and Life Insurance  
 Syphilis, Influence Upon Other Dis-  
   eases  
 Syphilis, Relation to Atrophic Cirrhosis  
 Syphilis, Studies in Experimental  
  
**T**AR Cancer and Liver Diet  
 Tapeworm, Broad  
 Tapeworm, Fish  
 Temporary Hyperthyroidism During  
   Insulin Treatment  
 Ten Hoor, M  
 Tetany, Pathogenesis of Gastrogenous  
 Therapy, Diabetic  
 Thermoregulatory Incompetency  
  
 1323 Thrombosis, Coronary  
 673 Thymoma of Lymphosarcoma Type  
 1114 Thyroid, Effect of Combined Feeding  
 341 Thyroid, Effect of Communicable Dis-  
 763 eases  
 692 Thyroid Medication  
 1309 Tobacco Angina  
 1253 Tolstoi, E  
 66 Torrey, J C  
 693 Toxic Adenoma and Exophthalmic  
 833 Goiter  
 1092 Toxin-Antitoxin Infection, Albumin-  
 97 uria and Nephritis  
 637 Toxins of B Welchii, Anemia follow-  
 973 ing Single Dose  
 1063, 1113 Transplantation of Testis  
 1300 Transposition of Viscera  
 97 Treatment of Acid Mouth  
 474 Treatment of Chronic Nephrosis  
 1198 Treatment of Dyspnea  
 Treatment of Encephalitis  
 Treatment of Endamebiasis  
 Treatment of Epilepsy by Ketogenic  
   Diet  
 Treatment of Gastric Ulcer, Medical  
 Treatment of Pneumonia with Potas-  
   sium Permanganate  
 Treatment, Preoperative of Graves'  
   Disease  
 Treatment of Rheumatic Fever  
 Treatment of Rheumatism  
 Tropical Sprue in Porto Rico  
 Tropics Influence on Rickets  
 Tuberculosis Clinical  
 Tuberculosis, Gastric  
 Tuberculosis, Intestinal  
 Tuberculosis Pathogenesis of  
 Tuberculosis, Pulmonary  
 Tuberculosis, Roentgenography in  
 Tularemia  
 Turner, T B  
  
 1114 **U**LCER, Gastric, Medical Treatment  
 693 of  
 113 Ulcerative Endocarditis of Pulmonic  
   Cusps  
 975 Undulant Fever in Connecticut  
 474 Undulant Fever Epidemic of  
 300 Undulant Fever in Iowa  
 269 Ureteral Stricture as Cause of At-  
 1113 tempted Suicide

- |  |  |  |            |
|--|--|--|------------|
| <b>V</b> ARIABLE Factors in Use of           |  | Weiss, C                               | 1198       |
| Wright's Stain                               | 289  | Weiss, E                               | 665        |
| Varicella, Specific Prophylactic Measures in | 518  | Weissenburg, T H                       | 104        |
| Vedder, E B                                  | 298  | Welch, A S                             | .456, 1194 |
| Veins, Measurements of Renal                 | 1047   | Weller, C V                            | 725        |
| Vergeer, Teunis                              | 693  | Whitmore, E R                          | 316        |
| Vining, C W                                  | 229  | Wilkes-Weiss, D                        | 1198       |
| Viscera, Transposition of                    | 963  | Wilson, W J                            | 669        |
| Vogt, E                                      | 976  | Workers in Dusty Trades                | 296        |
| Voigt, B                                     | 693  | Wright's Stain, Use of                 | 289        |
| Vomiting, Postinfluenzal                     | 1194   |  |            |
| Von Glahn, W C                               | 835  | <b>X</b> ANTHOMATOSIS, Generalized     | 689        |
|  |  | Xanthosis Diabetica, Action of Insulin | 1114       |
| <b>W</b> ARFIELD, L M                        | 446  |  |            |
| Warthin, A S                                 | 108, 222, 294, 373, 482, 553, 571, 689, 827, 968, 1108, 1223, 1346 | <b>Y</b> ELLOW Fever, Research in      | 138        |
| Webb, G B                                    | 56   | <b>Z</b> WICK, W W                     | 550        |

